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(54) Title: MODIFIED HIV ENV POLYPEPTIDES (57) Abstract Polynucleotide encoding modified HIV Env polypept of the CD4 binding region. Methods of diagnosis, treatme	ides are	disclosed. The Env polypeptides are modified so as to expose at least par prevention using the polynucleotides and polypeptides are also provided.

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MODIFIED HIV ENV POLYPEPTIDES

Technical Field

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The invention relates generally to modified HIV envelope (Env) polypeptides which are useful as immunizing agents or for generating an immune response in a subject, for example a cellular immune response or a protective immune response. More particularly, the invention relates Env polypeptides such as gp120, gp140 or gp160, wherein at least one of the native β-sheet configurations has been modified. The invention also pertains to methods of using these polypeptides to elicit an immune response against a broad range of HIV subtypes.

Background of the Invention

The human immunodeficiency virus (HIV-1, also referred to as HTLV-III, LAV or HTLV-III/LAV) is the etiological agent of the acquired immune deficiency syndrome (AIDS) and related disorders. (see, e.g., Barre-Sinoussi, et al., (1983) Science 220:868-871; Gallo et al. (1984) Science 224:500-503; Levy et al., (1984) Science 225:840-842; Siegal et al., (1981) N. Engl. J. Med. 305:1439-1444). AIDS patients usually have a long asymptomatic period followed by the progressive degeneration of the immune system and the central nervous system. Replication of the virus is highly regulated, and both latent and lytic infection of the CD4 positive helper subset of T-lymphocytes occur in tissue culture (Zagury et al., (1986) Science 231:850-853). Molecular studies of HIV-1 show that it encodes a number of genes (Ratner et al., (1985) Nature 313:277-284; Sanchez-Pescador et al., (1985) Science 227:484-492), including three structural genes -- gag, pol and env -- that are common to all retroviruses. Nucleotide sequences from viral genomes of other retroviruses, particularly HIV-2 and simian immunodeficiency viruses, SIV (previously referred to as STLV-III), also contain these structural genes. (Guyader et al., (1987) Nature 326:662-669; Chakrabarti et al., (1987) Nature

The envelope protein of HIV-1, HIV-2 and SIV is a glycoprotein of about 160 kd (gp160). During virus infection of the host cell, gp160 is cleaved by host cell proteases to form gp120 and the integral membrane protein, gp41. The gp41 portion is anchored in the

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membrane bilayer of virion, while the gp120 segment protrudes into the surrounding environment. gp120 and gp41 are more covalently associated and free gp120 can be released from the surface of virions and infected cells.

As depicted in Figure 1, crystallography studies of the gp120 core polypeptide indicate that this polypeptide is folded into two major domains having certain emanating structures. The inner domain (inner with respect to the N and C terminus) features a two-helix, two-stranded bundle with a small five-stranded β -sandwich at its termini-proximal end and a projection at the distal end from which the V1/V2 stem emanates. The outer domain is a staked double barrel that lies along side the inner domain so that the outer barrel and inner bundle axes are approximately parallel. Between the distal inner domain and the distal outer domain is a four-stranded bridging sheet which holds a peculiar minidomain in contact with, but distinct from, the inner, the outer domain, and the V1/V2 domain. The bridging sheet is composed of four β -strand structures (β -3, β -2, β -21, β -20, shown in Figure 1). The bridging region can be seen in Figure 1 packing primarily over the inner domain, although some surface residues of the outer domain, such as Phe 382, reach into the bridging sheet to form part of its hydrophobic core.

The basic unit of the β -sheet conformation of the bridging sheet region is the β -strand which exists as a less tightly coiled helix, with 2.0 residues per turn. The β -strand conformation is only stable when incorporated into a β -sheet, where hydrogen bonds with close to optimal geometry are formed between the peptide groups on adjacent β -strands; the dipole moments of the strands are also aligned favorably. Side chains from adjacent residues of the same strand protrude from opposite sides of the sheet and do not interact with each other, but have significant interactions with their backbone and with the side chains of neighboring strands. For a general description of β -sheets, see, e.g., T.E. Creighton, Proteins: Structures and Molecular Properties (W.H. Freeman and Company, 1993); and A.L. Lehninger, Biochemistry (Worth Publishers, Inc., 1975).

The gp120 polypeptide is instrumental in mediating entry into the host cell. Recent studies have indicated that binding of CD4 to gp120 induces a conformational change in Env that allows for binding to a co-receptor (e.g., a chemokine receptor) and subsequent entry of the virus into the cell. (Wyatt, R., et al. (1998) Nature 393:705-711; Kwong, P., et al. (1998) Nature 393:648-659). Referring again to Figure 1, CD4 is bound into a depression formed at the interface of the outer domain, the inner domain and the bridging sheet of gp120.

Immunogenicity of the gp120 polypeptide has also been studied. For example, individuals infected by HIV-1 usually develop antibodies that can neutralize the virus in in vitro assays, and this response is directed primarily against linear neutralizing determinants in the third variable loop of gp120 glycoprotein (Javaherian, K., et al. (1989) Proc. Natl. Acad. Sci. 86:6786-6772; Matsushita, M., et al. (1988) J. Virol. 62:2107-2144; Putney, S., et al. (1986) Science 234:1392-1395; Rushe, J. R., et al. (1988) Proc. Nat. Acad. Sci. USA 85: 3198-3202.). However, these antibodies generally exhibit the ability to neutralize only a limited number of HIV-1 strains (Matthews, T. (1986) Proc. Natl. Acad. Sci. USA 83:9709-9713; Nara, P. L., et al. (1988) J. Virol. 62:2622-2628; Palker, T. J., et al. (1988) Proc. Natl. Acad. Sci. USA 85:1932-1936). Later in the course of HIV infection in humans, antibodies capable of neutralizing a wider range of HIV-1 isolates appear (Barre-Sinoussi, F., et al. (1983) Science 220:868-871; Robert-Guroff, M., et al. (1985) Nature (London) 316:72-74; Weis, R., et al. (1985) Nature (London) 316:69-72; Weis, R., et al. (1986) Nature (London) 324:572-575).

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Recent work done by Stamatatos et al (1998) AIDS Res Hum Retroviruses 14(13):1129-39, shows that a deletion of the variable region 2 from a HIV-1_{SF162} virus, which utilizes the CCR-5 co-receptor for virus entry, rendered the virus highly susceptible to serum-mediated neutralization. This V2 deleted virus was also neutralized by sera obtained from patients infected not only with clade B HIV-1 isolates but also with clade A, C, D and F HIV-1 isolates. However, deletion of the variable region 1 had no effect. Deletion of the variable regions 1 and 2 from a LAI isolate HIV-I_{IIIB} also increased the susceptibility to neutralization by monoclonal antibodies whose epitopes are located within the V3 loop, the CD4-binding site, and conserved gp120 regions (Wyatt, R., et al. (1995) J Virol. 69:5723-5733). Rabbit immunogenicity studies done with the HIV-1 virus with deletions in the V1/V2 and V3 region from the LAI strain, which uses the CXCR4 co-receptor for virus entry, showed no improvement in the ability of Env to raise neutralizing antibodies (Leu et al. (1998) AIDS Res. and Human Retroviruses. 14:151-155).

Further, a subset of the broadly reactive antibodies, found in most infected individuals, interferes with the binding of gp120 and CD4 (Kang, C.-Y., et al. (1991) *Proc. Natl. Acad. Sci. USA.* 88:6171-6175; McDougal, J. S., et al. (1986) *J. Immunol.* 137:2937-2944). Other antibodies are believed to bind to the chemokine receptor binding region after CD4 has bound to Env (Thali et al. (1993) *J. Virol.* 67:3978-3988). The fact that neutralizing

antibodies generated during the course of HIV infection do not provide permanent antiviral effect may in part be due to the generation of "neutralization escapes" virus mutants and to the general decline in the host immune system associated with pathogenesis. In contrast, the presence of pre-existing neutralizing antibodies upon initial HIV-1 exposure will likely have a protective effect.

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It is widely thought that a successful vaccine should be able to induce a strong, broadly neutralizing antibody response against diverse HIV-1 strains (Montefiori and Evans (1999) AIDS Res. Hum. Ret. 15(8):689-698; Bolognesi, D.,P., et al. (1994) Ann. Int. Med. 8:603-611; Haynes, B., F., et al. (1996) Science; 271: 324-328.). Neutralizing antibodies, by attaching to the incoming virions, can reduce or even prevent their infectivity for target cells and prevent the cell-to-cell spread of virus in tissue culture (Hu et al. (1992) Science 255:456-459; Burton, D.,R. and Montefiori, D. (1997) AIDS 11(suppl. A): 587-598). However as described above, antibodies directed against gp120 do not generally exhibit broad antibody responses against different HIV strains.

Currently, the focus of vaccine development, from the perspective of humoral immunity, is on the neutralization of primary isolates that utilize the CCR5 chemokine coreceptor believed to be important in virus entry (Zhu, T., et al. (1993) *Science* 261:1179-1181; Fiore, J., et al. (1994) Virology; 204:297-303). These viruses are generally much more resistant to antibody neutralization than T-cell line adapted strains that use the CXCR4 coreceptor, although both can be neutralized *in vitro* by certain broadly and potent acting monoclonal antibodies, such as IgG1b12, 2G12 and 2F5 (Trkola, A., et al. (1995) *J. Virol*. 69:6609-6617; D'Sousa PM., et al (1997) *J. Infect. Dis.* 175:1062-1075). These monoclonal antibodies are directed to the CD4 binding site, a glycosylation site and to the gp41 fusion domain, respectively. The problem that remains, however, is that it is not known how to induce antibodies of the appropriate specificity by vaccination. Antibodies (Abs) elicited by gp120 glycoprotein from a given isolate are usually only able to neutralize closely related viruses generally from similar, usually from the same, HIV-1 subtype.

Despite the above approaches, there remains a need for Env antigens that can elicit an immunological response (e.g., neutralizing and/or protective antibodies) in a subject against multiple HIV strains and subtypes, for example when administered as a vaccine. The present invention solves these and other problems by providing modified Env polypeptides (e.g., gp120) to expose epitopes in or near the CD4 binding site.

Summary of the Invention

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In accordance with the present invention, modified HIV Env polypeptides are provided. In particular, deletions and/or mutations are made in one or more of the 4-β antiparallel-bridging sheet in the HIV Env polypeptide. In this way, enough structure is left to allow correct folding of the polypeptide, for example of gp120, yet enough of the bridging sheet is removed to expose the CD4 groove, allowing an immune response to be generated against epitopes in or near the CD4 binding site of the Env polypeptide (e.g., gp120).

In one aspect, the invention includes a polynucleotide encoding a modified HIV Env polypeptide wherein the polypeptide has at least one modified (e.g., deleted or replaced) amino acid residue deleted in the region corresponding to residues 421 to 436 relative to HXB-2, for example the constructs depicted in Figures 6-29 (SEQ ID NOs:3 to 26). In certain embodiments, the polynucleotide also has the region corresponding to residues 124-198 of the polypeptide HXB-2 (e.g., V1/V2) deleted and at least one amino acid deleted or replaced in the regions corresponding to the residues 119 to 123 and 199 to 210, relative to HXB-2. In other embodiments, these polynucleotides encode Env polypeptides having at least one amino acid of the small loop of the bridging sheet (e.g., amino acid residues 427 to 429 relative to HXB-2) deleted or replaced. The amino acid sequences of the modified polypeptides encoded by the polynucleotides of the present invention can be based on any HIV variant, for example SF162.

In another aspect, the invention includes immunogenic modified HIV Env polypeptides having at least one modified (e.g., deleted or replaced) amino acid residue deleted in the region corresponding to residues 421 to 436 relative to HXB-2, for example a deletion or replacement of one amino acids in the small loop region (e.g., amino acid residues 427 to 429 relative to HXB-2). These polypeptides may have modifications (e.g., a deletion or a replacement) of at least one amino acid between about amino acid residue 420 and amino acid residue 436, relative to HXB-2 and, optionally, may have deletions or truncations of the V1 and/or V2 regions. The immunogenic, modified polypeptides of the present invention can be based on any HIV variant, for example SF162.

In another aspect, the invention includes a vaccine composition comprising any of the polynucleotides encoding modified Env polypeptides described above. Vaccine compositions comprising the modified Env polypeptides and, optionally, an adjuvant are also included in the invention.

In yet another aspect, the invention includes a method of inducing an immune response in subject comprising, administering one or more of the polynucleotides or constructs described above in an amount sufficient to induce an immune response in the subject. In certain embodiments, the method further comprises administering an adjuvant to the subject.

In another aspect, the invention includes a method of inducing an immune response in a subject comprising administering a composition comprising any of the modified Env polypeptides described above and an adjuvant. The composition is administered in an amount sufficient to induce an immune response in the subject.

In another aspect, the invention includes a method of inducing an immune response in a subject comprising

- (a) administering a first composition comprising any of the polynucleotides described above in a priming step and
- (b) administering a second composition comprising any of the modified Env polypeptides described above, as a booster, in an amount sufficient to induce an immune response in the subject. In certain embodiments, the first composition, the second composition or both the first and second compositions further comprise an adjuvant.

These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein.

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Brief Description of the Drawings

Figure 1 is a schematic depiction of the tertiary structure of the HIV-1_{HXB-2} Env gp120 polypeptide, as determined by crystallography studies.

Figures 2A-C depict alignment of the amino acid sequence of wild-type HIV-1_{HXB-2} Env gp160 polypeptide (SEQ ID NO:1) with amino acid sequence of HIV variants SF162 (shown as "162") (SEQ ID NO:2), SF2, CM236 and US4. Arrows indicate the regions that are deleted or replaced in the modified polypeptides. Black dots indicate conserved cysteine residues. The star indicates the position of the last amino acid in gp120.

Figures 3A-J depict alignment of nucleotide sequences of polynucleotides encoding modified Env polypeptides having V1/V2 deletions. The unmodified amino acid residues encoded by these sequences correspond to wildtype SF162 residues but are numbered relative to HXB-2.

Figures 4A-M depict alignment of nucleotide sequences of polynucleotides encoding modified Env polypeptides having deletions or replacements in the small loop. The unmodified amino acid residues encoded by these sequences correspond to wildtype SF162 residues but are numbered relative to HXB-2.

Figures 5A-N depict alignment of nucleotide sequences of polynucleotides encoding modified Env polypeptides having both V1/V2 deletions and, in addition, deletions or replacements in the small loop. The unmodified amino acid residues encoded by these sequences correspond to wildtype SF162 residues but are numbered relative to HXB-2.

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Figure 6 depicts the nucleotide sequence of the construct designated Val120-Ala204 (SEQ ID NO:3).

Figure 7 depicts the nucleotide sequence of the construct designated Val120-Ile201 (SEQ ID NO:4).

Figure 8 depicts the nucleotide sequence of the construct designated Vall20-Ile201B (SEQ ID NO:5).

Figure 9 depicts the nucleotide sequence of the construct designated Lys121-Val200 (SEQ ID NO:6).

Figure 10 depicts the nucleotide sequence of the construct designated Leu122-Ser199 (SEQ ID NO:7).

Figure 11 depicts the nucleotide sequence of the construct designated Val120-Thr202 (SEQ ID NO:8).

Figure 12 depicts the nucleotide sequence of the construct designated Trp427-Gly431 (SEQ ID NO:9).

Figure 13 depicts the nucleotide sequence of the construct designated Arg426-Gly431 (SEQ ID NO:10).

Figure 14 depicts the nucleotide sequence of the construct designated Arg426-Gly431B (SEQ ID NO:11).

Figure 15 depicts the nucleotide sequence of the construct designated Arg426-Lys432 (SEQ ID NO:12).

Figure 16 depicts the nucleotide sequence of the construct designated Asn425-Lys432 (SEQ ID NO:13).

Figure 17 depicts the nucleotide sequence of the construct designated Ile424-Ala433 (SEQ ID NO:14).

Figure 18 depicts the nucleotide sequence of the construct designated Ile423-Met434 (SEQ ID NO:15).

Figure 19 depicts the nucleotide sequence of the construct designated Gln422-Tyr435 (SEQ ID NO:16).

Figure 20 depicts the nucleotide sequence of the construct designated Gln422-Tyr435B (SEQ ID NO:17).

Figure 21 depicts the nucleotide sequence of the construct designated Leu122-Ser199;Arg426-Gly431 (SEQ ID NO:18).

Figure 22 depicts the nucleotide sequence of the construct designated Leu122-Ser199;Arg426-Lys432 (SEQ ID NO:19).

Figure 23 depicts the nucleotide sequence of the construct designated Leu122-Ser199; Trp427-Gly431 (SEQ ID NO:20).

Figure 24 depicts the nucleotide sequence of the construct designated Lys121-Val200; Asn425-Lys432 (SEQ ID NO:21).

Figure 25 depicts the nucleotide sequence of the construct designated Val120-Ile201; Ile424-Ala433 (SEQ ID NO:22).

Figure 26 depicts the nucleotide sequence of the construct designated Val120-Ile201B; Ile424-Ala433 (SEQ ID NO:23).

Figure 27 depicts the nucleotide sequence of the construct designated Val120-Thr202; Ile424-Ala433 (SEQ ID NO:24).

Figure 28 depicts the nucleotide sequence of the construct designated Val127-Asn195 (SEQ ID NO:25).

Figure 29 depicts the nucleotide sequence of the construct designated Val127-Asn195; Arg426-Gly431 (SEQ ID NO:26).

Detailed Description of the Invention

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The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, viral immunobiology, molecular biology and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, <u>Proteins: Structures and Molecular Properties</u> (W.H. Freeman and Company, 1993); Nelson L.M. and Jerome H.K. <u>HIV Protocols</u> in Methods in Molecular Medicine, vol. 17, 1999; Sambrook, et al., <u>Molecular Cloning: A</u>

<u>Laboratory Manual</u> (Cold Spring Harbor Laboratory, 1989); F.M. Ausubel et al. <u>Current Protocols in Molecular Biology</u>, Greene Publishing Associates & Wiley Interscience New York; and Lipkowitz and Boyd, <u>Reviews in Computational Chemistry</u>, volumes 1-present (Wiley-VCH, New York, New York, 1999).

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "a polypeptide" includes a mixture of two or more polypeptides, and the like.

10 Definitions

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In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

The terms "polypeptide," and "protein" are used interchangeably herein to denote any polymer of amino acid residues. The terms encompass peptides, oligopeptides, dimers, multimers, and the like. Such polypeptides can be derived from natural sources or can be synthesized or recombinantly produced. The terms also include postexpression modifications of the polypeptide, for example, glycosylation, acetylation, phosphorylation, etc.

A polypeptide as defined herein is generally made up of the 20 natural amino acids Ala (A), Arg (R), Asn (N), Asp (D), Cys (C), Gln (Q), Glu (E), Gly (G), His (H), Ile (I), Leu (L), Lys (K), Met (M), Phe (F), Pro (P), Ser (S), Thr (T), Trp (W), Tyr (Y) and Val (V) and may also include any of the several known amino acid analogs, both naturally occurring and synthesized analogs, such as but not limited to homoisoleucine, asaleucine, 2-(methylenecyclopropyl)glycine, S-methylcysteine, S-(prop-l-enyl)cysteine, homoserine, ornithine, norleucine, norvaline, homoarginine, 3-(3-carboxyphenyl)alanine, cyclohexylalanine, mimosine, pipecolic acid, 4-methylglutamic acid, canavanine, 2,3-diaminopropionic acid, and the like. Further examples of polypeptide agents which will find use in the present invention are set forth below.

By "geometry" or "tertiary structure" of a polypeptide or protein is meant the overall 3-D configuration of the protein. As described herein, the geometry can be determined, for example, by crystallography studies or by using various programs or algorithms which predict the geometry based on interactions between the amino acids making up the primary and secondary structures.

By "wild type" polypeptide, polypeptide agent or polypeptide drug, is meant a naturally occurring polypeptide sequence, and its corresponding secondary structure. An "isolated" or "purified" protein or polypeptide is a protein which is separate and discrete from a whole organism with which the protein is normally associated in nature. It is apparent that the term denotes proteins of various levels of purity. Typically, a composition containing a purified protein will be one in which at least about 35%, preferably at least about 40-50%, more preferably, at least about 75-85%, and most preferably at least about 90% or more, of the total protein in the composition will be the protein in question.

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By "Env polypeptide" is meant a molecule derived from an envelope protein, preferably from HIV Env. The envelope protein of HIV-1 is a glycoprotein of about 160 kd (gp160). During virus infection of the host cell, gp160 is cleaved by host cell proteases to form gp120 and the integral membrane protein, gp41. The gp41 portion is anchored in (and spans) the membrane bilayer of virion, while the gp120 segment protrudes into the surrounding environment. As there is no covalent attachment between gp120 and gp41, free gp120 is released from the surface of virions and infected cells. Env polypeptides may also include gp140 polypeptides. Env polypeptides can exist as monomers, dimers or multimers.

By a "gp120 polypeptide" is meant a molecule derived from a gp120 region of the Env polypeptide. Preferably, the gp120 polypeptide is derived from HIV Env. The primary amino acid sequence of gp120 is approximately 511 amino acids, with a polypeptide core of about 60,000 daltons. The polypeptide is extensively modified by N-linked glycosylation to increase the apparent molecular weight of the molecule to 120,000 daltons. The amino acid sequence of gp120 contains five relatively conserved domains interspersed with five hypervariable domains. The positions of the 18 cysteine residues in the gp120 primary sequence of the HIV-1_{HXB-2} (hereinafter "HXB-2") strain, and the positions of 13 of the approximately 24 N-linked glycosylation sites in the gp120 sequence are common to most, if not all, gp120 sequences. The hypervariable domains contain extensive amino acid substitutions, insertions and deletions. Despite this variation, most, if not all, gp120 sequences preserve the virus's ability to bind to the viral receptor CD4. A "gp120 polypeptide" includes both single subunits or multimers.

Env polypeptides (e.g., gp120, gp140 and gp160) include a "bridging sheet" comprised of 4 anti-parallel β -strands (β -2, β -3, β -20 and β -21) that form a β -sheet. Extruding from one pair of the β -strands (β -2 and β -3) are two loops, V1 and V2. The β -2

sheet occurs at approximately amino acid residue 119 (Cys) to amino acid residue 123 (Thr) while β -3 occurs at approximately amino acid residue 199 (Ser) to amino acid residue 201 (Ile), relative to HXB-2. The "V1/V2 region" occurs at approximately amino acid positions 126 (Cys) to residue 196 (Cys), relative to HXB-2. (see, *e.g.*, Wyatt et al. (1995) *J. Virol.* 69:5723-5733; Stamatatos et al. (1998) *J. Virol.* 72:7840-7845). Extruding from the second pair of β -strands (β -20 and β -21) is a "small-loop" structure, also referred to herein as "the bridging sheet small loop." In HXB-2, β -20 extends from about amino acid residue 422 (Gln) to amino acid residue 426 (Met) while β -21 extends from about amino acid residue 430 (Val) to amino acid residue 435 (Tyr). In variant SF162, the Met-426 is an Arg (R) residue. The "small loop" extends from about amino acid residue 427 (Trp) through 429 (Lys), relative to HXB-2. A representative diagram of gp120 showing the bridging sheet, the small loop, and V1/V2 is shown in Figure 1. In addition, alignment of the amino acid sequences of Env polypeptide gp160 of selected variants is shown, relative to HXB-2, in Figures 2A-C.

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Furthermore, an "Env polypeptide" or "gp120 polypeptide" as defined herein is not limited to a polypeptide having the exact sequence described herein. Indeed, the HIV genome is in a state of constant flux and contains several variable domains which exhibit relatively high degrees of variability between isolates. It is readily apparent that the terms encompass Env (e.g., gp120) polypeptides from any of the identified HIV isolates, as well as newly identified isolates, and subtypes of these isolates. Descriptions of structural features are given herein with reference to HXB-2. One of ordinary skill in the art in view of the teachings of the present disclosure and the art can determine corresponding regions in other HIV variants (e.g., isolates HIV_{IIIb}, HIV_{SF2}, HIV-1_{SF162}, HIV-1_{SF170}, HIV_{LAV}, HIV_{LAI}, HIV_{MN}, HIV-1_{CM235},, HIV-1_{US4}, other HIV-1 strains from diverse subtypes(e.g., subtypes, A through G, and O), HIV-2 strains and diverse subtypes (e.g., HIV- 2_{UC1} and HIV- 2_{UC2}), and simian immunodeficiency virus (SIV). (See, e.g., Virology, 3rd Edition (W.K. Joklik ed. 1988); Fundamental Virology, 2nd Edition (B.N. Fields and D.M. Knipe, eds. 1991); Virology, 3rd Edition (Fields, BN, DM Knipe, PM Howley, Editors, 1996, Lippincott-Raven, Philadelphia, PA; for a description of these and other related viruses), using for example, sequence comparison programs (e.g., BLAST and others described herein) or identification and alignment of structural features (e.g., a program such as the "ALB" program described herein that can identify β-sheet regions). The actual amino acid sequences of the modified Env polypeptides can be based on any HIV variant.

Additionally, the term "Env polypeptide" (e.g., "gp120 polypeptide") encompasses proteins which include additional modifications to the native sequence, such as additional internal deletions, additions and substitutions. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through naturally occurring mutational events. Thus, for example, if the Env polypeptide is to be used in vaccine compositions, the modifications must be such that immunological activity (i.e., the ability to elicit an antibody response to the polypeptide) is not lost. Similarly, if the polypeptides are to be used for diagnostic purposes, such capability must be retained.

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Thus, a "modified Env polypeptide" is an Env polypeptide (e.g., gp120 as defined above), which has been manipulated to delete or replace all or a part of the bridging sheet portion and, optionally, the variable regions V1 and V2. Generally, modified Env (e.g., gp120) polypeptides have enough of the bridging sheet removed to expose the CD4 binding site, but leave enough of the structure to allow correct folding (e.g., correct geometry). Thus, modifications to the β -20 and β -21 regions (between about amino acid residues 420 and 435 relative to HXB-2) are preferred. Additionally, modifications to the β -2 and β -3 regions (between about amino acid residues 119 (Cys) and 201 (Ile)) and modifications (e.g., truncations) to the V1 and V2 loop regions may also be made. Although not all possible β -sheet and V1/V2 modifications have been exemplified herein, it is to be understood that other disrupting modifications are also encompassed by the present invention.

Normally, such a modified polypeptide is capable of secretion into growth medium in which an organism expressing the protein is cultured. However, for purposes of the present invention, such polypeptides may also be recovered intracellularly. Secretion into growth media is readily determined using a number of detection techniques, including, e.g., polyacrylamide gel electrophoresis and the like, and immunological techniques such as Western blotting and immunoprecipitation assays as described in, e.g., International Publication No. WO 96/04301, published February 15, 1996.

A gp120 or other Env polypeptide is produced "intracellularly" when it is found within the cell, either associated with components of the cell, such as in association with the endoplasmic reticulum (ER) or the Golgi Apparatus, or when it is present in the soluble cellular fraction. The gp120 and other Env polypeptides of the present invention may also be secreted into growth medium so long as sufficient amounts of the polypeptides remain

present within the cell such that they can be purified from cell lysates using techniques described herein.

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An "immunogenic" gp120 or other Env protein is a molecule that includes at least one epitope such that the molecule is capable of either eliciting an immunological reaction in an individual to which the protein is administered or, in the diagnostic context, is capable of reacting with antibodies directed against the HIV in question.

By "epitope" is meant a site on an antigen to which specific B cells and/or T cells respond, rendering the molecule including such an epitope capable of eliciting an immunological reaction or capable of reacting with HIV antibodies present in a biological sample. The term is also used interchangeably with "antigenic determinant" or "antigenic determinant site." An epitope can comprise 3 or more amino acids in a spatial conformation unique to the epitope. Generally, an epitope consists of at least 5 such amino acids and, more usually, consists of at least 8-10 such amino acids. Methods of determining spatial conformation of amino acids are known in the art and include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. Furthermore, the identification of epitopes in a given protein is readily accomplished using techniques well known in the art, such as by the use of hydrophobicity studies and by site-directed serology. See, also, Geysen et al., Proc. Natl. Acad. Sci. USA (1984) 81:3998-4002 (general method of rapidly synthesizing peptides to determine the location of immunogenic epitopes in a given antigen); U.S. Patent No. 4,708,871 (procedures for identifying and chemically synthesizing epitopes of antigens); and Geysen et al., Molecular Immunology (1986) 23:709-715 (technique for identifying peptides with high affinity for a given antibody). Antibodies that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen.

An "immunological response" or "immune response" as used herein is the development in the subject of a humoral and/or a cellular immune response to the Env (e.g., gp120) polypeptide when the polypeptide is present in a vaccine composition. These antibodies may also neutralize infectivity, and/or mediate antibody-complement or antibody dependent cell cytotoxicity to provide protection to an immunized host. Immunological reactivity may be determined in standard immunoassays, such as a competition assays, well known in the art.

Techniques for determining amino acid sequence "similarity" are well known in the art. In general, "similarity" means the exact amino acid to amino acid comparison of two or more polypeptides at the appropriate place, where amino acids are identical or possess similar chemical and/or physical properties such as charge or hydrophobicity. A so-termed "percent similarity" then can be determined between the compared polypeptide sequences.

Techniques for determining nucleic acid and amino acid sequence identity also are well known in the art and include determining the nucleotide sequence of the mRNA for that gene (usually via a cDNA intermediate) and determining the amino acid sequence encoded thereby, and comparing this to a second amino acid sequence. In general, "identity" refers to an exact nucleotide to nucleotide or amino acid to amino acid correspondence of two polynucleotides or polypeptide sequences, respectively.

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Two or more polynucleotide sequences can be compared by determining their "percent identity." Two or more amino acid sequences likewise can be compared by determining their "percent identity." The percent identity of two sequences, whether nucleic acid or peptide sequences, is generally described as the number of exact matches between two aligned sequences divided by the length of the shorter sequence and multiplied by 100. An approximate alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman, Advances in Applied Mathematics 2:482-489 (1981). This algorithm can be extended to use with peptide sequences using the scoring matrix developed by Dayhoff, Atlas of Protein Sequences and Structure, M.O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA, and normalized by Gribskov, Nucl. Acids Res. 14(6):6745-6763 (1986). An implementation of this algorithm for nucleic acid and peptide sequences is provided by the Genetics Computer Group (Madison, WI) in their BestFit utility application. The default parameters for this method are described in the Wisconsin Sequence Analysis Package Program Manual, Version 8 (1995) (available from Genetics Computer Group, Madison, WI). Other equally suitable programs for calculating the percent identity or similarity between sequences are generally known in the art.

For example, percent identity of a particular nucleotide sequence to a reference sequence can be determined using the homology algorithm of Smith and Waterman with a default scoring table and a gap penalty of six nucleotide positions. Another method of establishing percent identity in the context of the present invention is to use the MPSRCH

package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and distributed by IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages, the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a gap of six). From the data generated, the "Match" value reflects "sequence identity." Other suitable programs for calculating the percent identity or similarity between sequences are generally known in the art, such as the alignment program BLAST, which can also be used with default parameters. For example, BLASTN and BLASTP can be used with the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found at the following internet address: http://www.ncbi.nlm.gov/cgi-bin/BLAST.

One of skill in the art can readily determine the proper search parameters to use for a given sequence in the above programs. For example, the search parameters may vary based on the size of the sequence in question. Thus, for example, a representative embodiment of the present invention would include an isolated polynucleotide having X contiguous nucleotides, wherein (i) the X contiguous nucleotides have at least about 50% identity to Y contiguous nucleotides derived from any of the sequences described herein, (ii) X equals Y, and (iii) X is greater than or equal to 6 nucleotides and up to 5000 nucleotides, preferably greater than or equal to 8 nucleotides and up to 5000 nucleotides, more preferably 10-12 nucleotides and up to 5000 nucleotides, and even more preferably 15-20 nucleotides, up to the number of nucleotides present in the full-length sequences described herein (e.g., see the Sequence Listing and claims), including all integer values falling within the above-described ranges.

The synthetic expression cassettes (and purified polynucleotides) of the present invention include related polynucleotide sequences having about 80% to 100%, greater than 80-85%, preferably greater than 90-92%, more preferably greater than 95%, and most preferably greater than 98% sequence (including all integer values falling within these described ranges) identity to the synthetic expression cassette sequences disclosed herein (for example, to the claimed sequences or other sequences of the present invention) when the sequences of the present invention are used as the query sequence.

Computer programs are also available to determine the likelihood of certain polypeptides to form structures such as β-sheets. One such program, described herein, is the "ALB" program for protein and polypeptide secondary structure calculation and predication. In addition, secondary protein structure can be predicted from the primary amino acid sequence, for example using protein crystal structure and aligning the protein sequence related to the crystal structure (e.g., using Molecular Operating Environment (MOE) programs available from the Chemical Computing Group Inc., Montreal, P.Q., Canada). Other methods of predicting secondary structures are described, for example, in Garnier et al. (1996) Methods Enzymol. 266:540-553; Geourjon et al. (1995) Comput. Applic. Biosci. 11:681-684; Levin (1997) Protein Eng. 10:771-776; and Rost et al. (1993) J. Molec. Biol. 232:584-599.

Homology can also be determined by hybridization of polynucleotides under conditions which form stable duplexes between homologous regions, followed by digestion with single-stranded-specific nuclease(s), and size determination of the digested fragments. Two DNA, or two polypeptide sequences are "substantially homologous" to each other when the sequences exhibit at least about 80%-85%, preferably at least about 90%, and most preferably at least about 95%-98% sequence identity over a defined length of the molecules, as determined using the methods above. As used herein, substantially homologous also refers to sequences showing complete identity to the specified DNA or polypeptide sequence. DNA sequences that are substantially homologous can be identified in a Southern hybridization experiment under, for example, stringent conditions, as defined for that particular system. Defining appropriate hybridization conditions is within the skill of the art. See, e.g., Sambrook et al., supra; DNA Cloning, supra; Nucleic Acid Hybridization, supra.

A "coding sequence" or a sequence which "encodes" a selected protein, is a nucleic acid sequence which is transcribed (in the case of DNA) and translated (in the case of mRNA) into a polypeptide *in vitro* or *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxy) terminus. A coding sequence can include, but is not limited to cDNA from viral nucleotide sequences as well as synthetic and semisynthetic DNA sequences and sequences including base analogs. A transcription termination sequence may be located 3' to the coding sequence.

"Control elements" refers collectively to promoter sequences, ribosome binding sites, polyadenylation signals, transcription termination sequences, upstream regulatory domains, enhancers, and the like, which collectively provide for the transcription and translation of a coding sequence in a host cell. Not all of these control elements need always be present so long as the desired gene is capable of being transcribed and translated.

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A control element "directs the transcription" of a coding sequence in a cell when RNA polymerase will bind the promoter sequence and transcribe the coding sequence into mRNA, which is then translated into the polypeptide encoded by the coding sequence.

"Operably linked" refers to an arrangement of elements wherein the components so described are configured so as to perform their usual function. Thus, control elements operably linked to a coding sequence are capable of effecting the expression of the coding sequence when RNA polymerase is present. The control elements need not be contiguous with the coding sequence, so long as they function to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between, e.g., a promoter sequence and the coding sequence and the promoter sequence can still be considered "operably linked" to the coding sequence.

"Recombinant" as used herein to describe a nucleic acid molecule means a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which, by virtue of its origin or manipulation: (1) is not associated with all or a portion of the polynucleotide with which it is associated in nature; and/or (2) is linked to a polynucleotide other than that to which it is linked in nature. The term "recombinant" as used with respect to a protein or polypeptide means a polypeptide produced by expression of a recombinant polynucleotide. "Recombinant host cells," "host cells," "cells," "cell lines," "cell cultures," and other such terms denoting procaryotic microorganisms or eucaryotic cell lines cultured as unicellular entities, are used interchangeably, and refer to cells which can be, or have been, used as recipients for recombinant vectors or other transfer DNA, and include the progeny of the original cell which has been transfected. It is understood that the progeny of a single parental cell may not necessarily be completely identical in morphology or in genomic or total DNA complement to the original parent, due to accidental or deliberate mutation. Progeny of the parental cell which are sufficiently similar to the parent to be characterized by the relevant property, such as the presence of a nucleotide sequence encoding a desired peptide, are included in the progeny intended by this definition, and are covered by the above terms.

By "vertebrate subject" is meant any member of the subphylum chordata, including, without limitation, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The term does not denote a particular age. Thus, both adult and newborn individuals are intended to be covered.

As used herein, a "biological sample" refers to a sample of tissue or fluid isolated from an individual, including but not limited to, for example, blood, plasma, serum, fecal matter, urine, bone marrow, bile, spinal fluid, lymph fluid, samples of the skin, external secretions of the skin, respiratory, intestinal, and genitourinary tracts, samples derived from the gastric epithelium and gastric mucosa, tears, saliva, milk, blood cells, organs, biopsies and also samples of *in vitro* cell culture constituents including but not limited to conditioned media resulting from the growth of cells and tissues in culture medium, e.g., recombinant cells, and cell components.

The terms "label" and "detectable label" refer to a molecule capable of detection, including, but not limited to, radioactive isotopes, fluorescers, chemiluminescers, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chromophores, dyes, metal ions, metal sols, ligands (e.g., biotin or haptens) and the like. The term "fluorescer" refers to a substance or a portion thereof which is capable of exhibiting fluorescence in the detectable range. Particular examples of labels which may be used with the invention include, but are not limited to fluorescein, rhodamine, dansyl, umbelliferone, Texas red, luminol, acradimum esters, NADPH, α - β -galactosidase, horseradish peroxidase, glucose oxidase, alkaline phosphatase and urease.

Overview

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The present invention concerns modified Env polypeptide molecules (e.g., glycoprotein ("gp") 120). Without being bound by a particular theory, it appears that it has been difficult to generate immunological responses against Env because the CD4 binding site is buried between the outer domain, the inner domain and the V1/V2 domains. Thus, although deletion of the V1/V2 domain may render the virus more susceptible to

neutralization by monoclonal antibody directed to the CD4 site, the bridging sheet covering most of the CD4 binding domain may prevent an antibody response. Thus, the present invention provides Env polypeptides that maintain their general overall structure yet expose the CD4 binding domain. This allows the generation of an immune response (e.g., an antibody response) to epitopes in or near the CD4 binding site.

Various forms of the different embodiments of the invention, described herein, may be combined.

β-Sheet Conformations

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In the present invention, location of the β -sheet structures were identified relative to 3-D (crystal) structure of an HXB-2 crystallized Env protein (see, Example 1A). Based on this structure, constructs encoding polypeptides having replacements and or excisions which maintain overall geometry while exposing the CD4 binding site were designed. In particular, the crystal structure of HXB-2 was downloaded from the Brookhaven Database. Using the default parameters of the Loop Search feature of the Biopolymer module of the Sybyl molecular modeling package, homology and fit of amino acids which could replace the native loops between β -strands yet maintain overall tertiary structure were determined. Constructs encoding the modified Env polypeptides were then designed (Example 1.B.).

Thus, the modified Env polypeptides typically have enough of the bridging sheet removed to expose the CD4 groove, but have enough of the structure to allow correct folding of the Env glycoprotein. Exemplary constructs are described below.

Polypeptide Production

The polypeptides of the present invention can be produced in any number of ways which are well known in the art.

In one embodiment, the polypeptides are generated using recombinant techniques, well known in the art. In this regard, oligonucleotide probes can be devised based on the known sequences of the Env (e.g., gp120) polypeptide genome and used to probe genomic or cDNA libraries for Env genes. The gene can then be further isolated using standard techniques and, e.g., restriction enzymes employed to truncate the gene at desired portions of the full-length sequence. Similarly, the Env gene(s) can be isolated directly from cells and tissues containing the same, using known techniques, such as phenol extraction and the

sequence further manipulated to produce the desired truncations. See, e.g., Sambrook et al., supra, for a description of techniques used to obtain and isolate DNA.

The genes encoding the modified (e.g., truncated and/or substituted) polypeptides can be produced synthetically, based on the known sequences. The nucleotide sequence can be designed with the appropriate codons for the particular amino acid sequence desired. The complete sequence is generally assembled from overlapping oligonucleotides prepared by standard methods and assembled into a complete coding sequence. See, e.g., Edge (1981) Nature 292:756; Nambair et al. (1984) Science 223:1299; Jay et al. (1984) J. Biol. Chem. 259:6311; Stemmer et al. (1995) Gene 164:49-53.

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Recombinant techniques are readily used to clone a gene encoding an Env polypeptide gene which can then be mutagenized *in vitro* by the replacement of the appropriate base pair(s) to result in the codon for the desired amino acid. Such a change can include as little as one base pair, effecting a change in a single amino acid, or can encompass several base pair changes. Alternatively, the mutations can be effected using a mismatched primer which hybridizes to the parent nucleotide sequence (generally cDNA corresponding to the RNA sequence), at a temperature below the melting temperature of the mismatched duplex. The primer can be made specific by keeping primer length and base composition within relatively narrow limits and by keeping the mutant base centrally located. See, *e.g.*, Innis et al, (1990) PCR Applications: Protocols for Functional Genomics; Zoller and Smith, *Methods Enzymol.* (1983) 100:468. Primer extension is effected using DNA polymerase, the product cloned and clones containing the mutated DNA, derived by segregation of the primer extended strand, selected. Selection can be accomplished using the mutant primer as a hybridization probe. The technique is also applicable for generating multiple point mutations. See, e.g., Dalbie-McFarland et al. *Proc. Natl. Acad. Sci USA* (1982) 79:6409.

Once coding sequences for the desired proteins have been isolated or synthesized, they can be cloned into any suitable vector or replicon for expression. As will be apparent from the teachings herein, a wide variety of vectors encoding modified polypeptides can be generated by creating expression constructs which operably link, in various combinations, polynucleotides encoding Env polypeptides having deletions or mutation therein. Thus, polynucleotides encoding a particular deleted V1/V2 region can be operably linked with polynucleotides encoding polypeptides having deletions or replacements in the small loop

region and the construct introduced into a host cell for polypeptide expression. Non-limiting examples of such combinations are discussed in the Examples.

Numerous cloning vectors are known to those of skill in the art, and the selection of an appropriate cloning vector is a matter of choice. Examples of recombinant DNA vectors for cloning and host cells which they can transform include the bacteriophage λ (E. coli), pBR322 (E. coli), pACYC177 (E. coli), pKT230 (gram-negative bacteria), pGV1106 (gram-negative bacteria), pLAFR1 (gram-negative bacteria), pME290 (non-E. coli gram-negative bacteria), pHV14 (E. coli and Bacillus subtilis), pBD9 (Bacillus), pIJ61 (Streptomyces), pUC6 (Streptomyces), YIp5 (Saccharomyces), YCp19 (Saccharomyces) and bovine papilloma virus (mammalian cells). See, generally, DNA Cloning: Vols. I & II, supra; Sambrook et al., supra; B. Perbal, supra.

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Insect cell expression systems, such as baculovirus systems, can also be used and are known to those of skill in the art and described in, e.g., Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987). Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, inter alia, Invitrogen, San Diego CA ("MaxBac" kit).

Plant expression systems can also be used to produce the modified Env proteins. Generally, such systems use virus-based vectors to transfect plant cells with heterologous genes. For a description of such systems see, e.g., Porta et al., *Mol. Biotech.* (1996) <u>5</u>:209-221; and Hackland et al., *Arch. Virol.* (1994) <u>139</u>:1-22.

Viral systems, such as a vaccinia based infection/transfection system, as described in Tomei et al., J. Virol. (1993) 67:4017-4026 and Selby et al., J. Gen. Virol. (1993) 74:1103-1113, will also find use with the present invention. In this system, cells are first transfected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the DNA of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into protein by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation product(s).

The gene can be placed under the control of a promoter, ribosome binding site (for bacterial expression) and, optionally, an operator (collectively referred to herein as "control" elements), so that the DNA sequence encoding the desired Env polypeptide is transcribed into RNA in the host cell transformed by a vector containing this expression construction. The coding sequence may or may not contain a signal peptide or leader sequence. With the present invention, both the naturally occurring signal peptides or heterologous sequences can be used. Leader sequences can be removed by the host in post-translational processing. See, e.g., U.S. Patent Nos. 4,431,739; 4,425,437; 4,338,397. Such sequences include, but are not limited to, the TPA leader, as well as the honey bee mellitin signal sequence.

Other regulatory sequences may also be desirable which allow for regulation of expression of the protein sequences relative to the growth of the host cell. Such regulatory sequences are known to those of skill in the art, and examples include those which cause the expression of a gene to be turned on or off in response to a chemical or physical stimulus, including the presence of a regulatory compound. Other types of regulatory elements may also be present in the vector, for example, enhancer sequences.

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The control sequences and other regulatory sequences may be ligated to the coding sequence prior to insertion into a vector. Alternatively, the coding sequence can be cloned directly into an expression vector which already contains the control sequences and an appropriate restriction site.

In some cases it may be necessary to modify the coding sequence so that it may be attached to the control sequences with the appropriate orientation; i.e., to maintain the proper reading frame. Mutants or analogs may be prepared by the deletion of a portion of the sequence encoding the protein, by insertion of a sequence, and/or by substitution of one or more nucleotides within the sequence. Techniques for modifying nucleotide sequences, such as site-directed mutagenesis, are well known to those skilled in the art. See, e.g., Sambrook et al., supra; DNA Cloning, Vols. I and II, supra; Nucleic Acid Hybridization, supra.

The expression vector is then used to transform an appropriate host cell. A number of mammalian cell lines are known in the art and include immortalized cell lines available from the American Type Culture Collection (ATCC), such as, but not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), Vero293 cells, as well as others. Similarly, bacterial hosts such as *E. coli*, *Bacillus subtilis*, and *Streptococcus spp.*, will find

use with the present expression constructs. Yeast hosts useful in the present invention include inter alia, Saccharomyces cerevisiae, Candida albicans, Candida maltosa, Hansenula polymorpha, Kluyveromyces fragilis, Kluyveromyces lactis, Pichia guillerimondii, Pichia pastoris, Schizosaccharomyces pombe and Yarrowia lipolytica. Insect cells for use with baculovirus expression vectors include, inter alia, Aedes aegypti, Autographa californica, Bombyx mori, Drosophila melanogaster, Spodoptera frugiperda, and Trichoplusia ni.

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Depending on the expression system and host selected, the proteins of the present invention are produced by growing host cells transformed by an expression vector described above under conditions whereby the protein of interest is expressed. The selection of the appropriate growth conditions is within the skill of the art.

In one embodiment, the transformed cells secrete the polypeptide product into the surrounding media. Certain regulatory sequences can be included in the vector to enhance secretion of the protein product, for example using a tissue plasminogen activator (TPA) leader sequence, a γ-interferon signal sequence or other signal peptide sequences from known secretory proteins. The secreted polypeptide product can then be isolated by various techniques described herein, for example, using standard purification techniques such as but not limited to, hydroxyapatite resins, column chromatography, ion-exchange chromatography, size-exclusion chromatography, electrophoresis, HPLC, immunoadsorbent techniques, affinity chromatography, immunoprecipitation, and the like..

Alternatively, the transformed cells are disrupted, using chemical, physical or mechanical means, which lyse the cells yet keep the Env polypeptides substantially intact. Intracellular proteins can also be obtained by removing components from the cell wall or membrane, e.g., by the use of detergents or organic solvents, such that leakage of the Env polypeptides occurs. Such methods are known to those of skill in the art and are described in, e.g., *Protein Purification Applications: A Practical Approach*, (E.L.V. Harris and S. Angal, Eds., 1990)

For example, methods of disrupting cells for use with the present invention include but are not limited to: sonication or ultrasonication; agitation; liquid or solid extrusion; heat treatment; freeze-thaw; desiccation; explosive decompression; osmotic shock; treatment with lytic enzymes including proteases such as trypsin, neuraminidase and lysozyme; alkali treatment; and the use of detergents and solvents such as bile salts, sodium dodecylsulphate,

Triton, NP40 and CHAPS. The particular technique used to disrupt the cells is largely a matter of choice and will depend on the cell type in which the polypeptide is expressed, culture conditions and any pre-treatment used.

Following disruption of the cells, cellular debris is removed, generally by centrifugation, and the intracellularly produced Env polypeptides are further purified, using standard purification techniques such as but not limited to, column chromatography, ion-exchange chromatography, size-exclusion chromatography, electrophoresis, HPLC, immunoadsorbent techniques, affinity chromatography, immunoprecipitation, and the like.

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For example, one method for obtaining the intracellular Env polypeptides of the present invention involves affinity purification, such as by immunoaffinity chromatography using anti-Env specific antibodies, or by lectin affinity chromatography. Particularly preferred lectin resins are those that recognize mannose moieties such as but not limited to resins derived from *Galanthus nivalis* agglutinin (GNA), *Lens culinaris* agglutinin (LCA or lentil lectin), *Pisum sativum* agglutinin (PSA or pea lectin), *Narcissus pseudonarcissus* agglutinin (NPA) and *Allium ursinum* agglutinin (AUA). The choice of a suitable affinity resin is within the skill in the art. After affinity purification, the Env polypeptides can be further purified using conventional techniques well known in the art, such as by any of the techniques described above.

It may be desirable to produce Env (e.g., gp120) complexes, either with itself or other proteins. Such complexes are readily produced by e.g., co-transfecting host cells with constructs encoding for the Env (e.g., gp120) and/or other polypeptides of the desired complex. Co-transfection can be accomplished either in trans or cis, i.e., by using separate vectors or by using a single vector which bears both of the Env and other gene. If done using a single vector, both genes can be driven by a single set of control elements or, alternatively, the genes can be present on the vector in individual expression cassettes, driven by individual control elements. Following expression, the proteins will spontaneously associate.

Alternatively, the complexes can be formed by mixing the individual proteins together which have been produced separately, either in purified or semi-purified form, or even by mixing culture media in which host cells expressing the proteins, have been cultured. See, International Publication No. WO 96/04301, published February 15, 1996, for a description of such complexes.

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Relatively small polypeptides, i.e., up to about 50 amino acids in length, can be conveniently synthesized chemically, for example by any of several techniques that are known to those skilled in the peptide art. In general, these methods employ the sequential addition of one or more amino acids to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected or derivatized amino acid can then be either attached to an inert solid support or utilized in solution by adding the next amino acid in the sequence having the complementary (amino or carboxyl) group suitably protected, under conditions that allow for the formation of an amide linkage. The protecting group is then removed from the newly added amino acid residue and the next amino acid (suitably protected) is then added, and so forth. After the desired amino acids have been linked in the proper sequence, any remaining protecting groups (and any solid support, if solid phase synthesis techniques are used) are removed sequentially or concurrently, to render the final polypeptide. By simple modification of this general procedure, it is possible to add more than one amino acid at a time to a growing chain, for example, by coupling (under conditions which do not racemize chiral centers) a protected tripeptide with a properly protected dipeptide to form, after deprotection, a pentapeptide. See, e.g., J. M. Stewart and J. D. Young, Solid Phase Peptide Synthesis (Pierce Chemical Co., Rockford, IL 1984) and G. Barany and R. B. Merrifield, The Peptides: Analysis, Synthesis, Biology, editors E. Gross and J. Meienhofer, Vol. 2, (Academic Press, New York, 1980), pp. 3-254, for solid phase peptide synthesis techniques; and M. Bodansky, Principles of Peptide Synthesis, (Springer-Verlag, Berlin 1984) and E. Gross and J. Meienhofer, Eds., The Peptides: Analysis, Synthesis, Biology, Vol. 1, for classical solution synthesis.

Typical protecting groups include t-butyloxycarbonyl (Boc), 9
fluorenylmethoxycarbonyl (Fmoc) benzyloxycarbonyl (Cbz); p-toluenesulfonyl (Tx); 2,4dinitrophenyl; benzyl (Bzl); biphenylisopropyloxycarboxy-carbonyl, tamyloxycarbonyl, isobornyloxycarbonyl, o-bromobenzyloxycarbonyl, cyclohexyl, isopropyl,
acetyl, o-nitrophenylsulfonyl and the like.

Typical solid supports are cross-linked polymeric supports. These can include divinylbenzene cross-linked-styrene-based polymers, for example, divinylbenzene-hydroxymethylstyrene copolymers, divinylbenzene-chloromethylstyrene copolymers and divinylbenzene-benzhydrylaminopolystyrene copolymers.

The polypeptide analogs of the present invention can also be chemically prepared by other methods such as by the method of simultaneous multiple peptide synthesis. See, e.g., Houghten *Proc. Natl. Acad. Sci. USA* (1985) 82:5131-5135; U.S. Patent No. 4,631,211.

Diagnostic and Vaccine Applications

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The intracellularly produced Env polypeptides of the present invention, complexes thereof, or the polynucleotides coding therefor, can be used for a number of diagnostic and therapeutic purposes. For example, the proteins and polynucleotides or antibodies generated against the same, can be used in a variety of assays, to determine the presence of reactive antibodies/and or Env proteins in a biological sample to aid in the diagnosis of HIV infection or disease status or as measure of response to immunization.

The presence of antibodies reactive with the Env (e.g., gp120) polypeptides and, conversely, antigens reactive with antibodies generated thereto, can be detected using standard electrophoretic and immunodiagnostic techniques, including immunoassays such as competition, direct reaction, or sandwich type assays. Such assays include, but are not limited to, western blots; agglutination tests; enzyme-labeled and mediated immunoassays, such as ELISAs; biotin/avidin type assays; radioimmunoassays; immunoelectrophoresis; immunoprecipitation, etc. The reactions generally include revealing labels such as fluorescent, chemiluminescent, radioactive, or enzymatic labels or dye molecules, or other methods for detecting the formation of a complex between the antigen and the antibody or antibodies reacted therewith.

Solid supports can be used in the assays such as nitrocellulose, in membrane or microtiter well form; polyvinylchloride, in sheets or microtiter wells; polystyrene latex, in beads or microtiter plates; polyvinylidine fluoride; diazotized paper; nylon membranes; activated beads, and the like.

Typically, the solid support is first reacted with the biological sample (or the gp120 proteins), washed and then the antibodies, (or a sample suspected of containing antibodies), applied. After washing to remove any non-bound ligand, a secondary binder moiety is added under suitable binding conditions, such that the secondary binder is capable of associating selectively with the bound ligand. The presence of the secondary binder can then be detected using techniques well known in the art. Typically, the secondary binder will comprise an antibody directed against the antibody ligands. A number of anti-human immunoglobulin

(Ig) molecules are known in the art (e.g., commercially available goat anti-human Ig or rabbit anti-human Ig). Ig molecules for use herein will preferably be of the IgG or IgA type, however, IgM may also be appropriate in some instances. The Ig molecules can be readily conjugated to a detectable enzyme label, such as horseradish peroxidase, glucose oxidase, Beta-galactosidase, alkaline phosphatase and urease, among others, using methods known to those of skill in the art. An appropriate enzyme substrate is then used to generate a detectable signal.

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Alternatively, a "two antibody sandwich" assay can be used to detect the proteins of the present invention. In this technique, the solid support is reacted first with one or more of the antibodies directed against Env (e.g., gp120), washed and then exposed to the test sample. Antibodies are again added and the reaction visualized using either a direct color reaction or using a labeled second antibody, such as an anti-immunoglobulin labeled with horseradish peroxidase, alkaline phosphatase or urease.

Assays can also be conducted in solution, such that the viral proteins and antibodies thereto form complexes under precipitating conditions. The precipitated complexes can then be separated from the test sample, for example, by centrifugation. The reaction mixture can be analyzed to determine the presence or absence of antibody-antigen complexes using any of a number of standard methods, such as those immunodiagnostic methods described above.

The modified Env proteins, produced as described above, or antibodies to the proteins, can be provided in kits, with suitable instructions and other necessary reagents, in order to conduct immunoassays as described above. The kit can also contain, depending on the particular immunoassay used, suitable labels and other packaged reagents and materials (i.e. wash buffers and the like). Standard immunoassays, such as those described above, can be conducted using these kits.

The Env polypeptides and polynucleotides encoding the polypeptides can also be used in vaccine compositions, individually or in combination, in e.g., prophylactic (i.e., to prevent infection) or therapeutic (to treat HIV following infection) vaccines. The vaccines can comprise mixtures of one or more of the modified Env proteins (or nucleotide sequences encoding the proteins), such as Env (e.g., gp120) proteins derived from more than one viral isolate. The vaccine may also be administered in conjunction with other antigens and immunoregulatory agents, for example, immunoglobulins, cytokines, lymphokines, and chemokines, including but not limited to IL-2, modified IL-2 (cys125-ser125), GM-CSF, IL-

12, γ-interferon, IP-10, MIP1β and RANTES. The vaccines may be administered as polypeptides or, alternatively, as naked nucleic acid vaccines (e.g., DNA), using viral vectors (e.g., retroviral vectors, adenoviral vectors, adeno-associated viral vectors) or non-viral vectors (e.g., liposomes, particles coated with nucleic acid or protein). The vaccines may also comprise a mixture of protein and nucleic acid, which in turn may be delivered using the same or different vehicles. The vaccine may be given more than once (e.g., a "prime" administration followed by one or more "boosts") to achieve the desired effects. The same composition can be administered as the prime and as the one or more boosts. Alternatively, different compositions can be used for priming and boosting.

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The vaccines will generally include one or more "pharmaceutically acceptable excipients or vehicles" such as water, saline, glycerol, ethanol, etc. Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present in such vehicles.

A carrier is optionally present which is a molecule that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycollic acids, polymeric amino acids, amino acid copolymers, lipid aggregates (such as oil droplets or liposomes), and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Furthermore, the Env polypeptide may be conjugated to a bacterial toxoid, such as toxoid from diphtheria, tetanus, cholera, etc.

Adjuvants may also be used to enhance the effectiveness of the vaccines. Such adjuvants include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc.; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (International Publication No. WO 90/14837), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE (see below), although not required) formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size

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emulsion, and (c) RibiTM adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM); (3) saponin adjuvants, such as Stimulon™ (Cambridge Bioscience, Worcester, MA) may be used or particle generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freunds Adjuvant (CFA) and Incomplete Freunds Adjuvant (IFA); (5) cytokines, such as interleukins (IL-1, IL-2, etc.), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; (6) detoxified mutants of a bacterial ADP-ribosylating toxin such as a cholera toxin (CT), a pertussis toxin (PT), or an E. coli heat-labile toxin (LT), particularly LT-K63 (where lysine is substituted for the wild-type amino acid at position 63) LT-R72 (where arginine is substituted for the wild-type amino acid at position 72), CT-S109 (where serine is substituted for the wild-type amino acid at position 109), and PT-K9/G129 (where lysine is substituted for the wild-type amino acid at position 9 and glycine substituted at position 129) (see, e.g., International Publication Nos. W093/13202 and W092/19265); and (7) other substances that act as immunostimulating agents to enhance the effectiveness of the composition.

Muramyl peptides include, but are not limited to, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acteyl-normuramyl-L-alanyl-D-isogluatme (nor-MDP), N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-sn-glycero-3-huydroxyphosphoryloxy)-ethylamine (MTP-PE), etc.

Typically, the vaccine compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation also may be emulsified or encapsulated in liposomes for enhanced adjuvant effect, as discussed above.

The vaccines will comprise a therapeutically effective amount of the modified Env proteins, or complexes of the proteins, or nucleotide sequences encoding the same, and any other of the above-mentioned components, as needed. By "therapeutically effective amount" is meant an amount of a modified Env (e.g., gp120) protein which will induce a protective immunological response in the uninfected, infected or unexposed individual to which it is administered. Such a response will generally result in the development in the subject of a secretory, cellular and/or antibody-mediated immune response to the vaccine. Usually, such

a response includes but is not limited to one or more of the following effects; the production of antibodies from any of the immunological classes, such as immunoglobulins A, D, E, G or M; the proliferation of B and T lymphocytes; the provision of activation, growth and differentiation signals to immunological cells; expansion of helper T cell, suppressor T cell, and/or cytotoxic T cell.

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Preferably, the effective amount is sufficient to bring about treatment or prevention of disease symptoms. The exact amount necessary will vary depending on the subject being treated; the age and general condition of the individual to be treated; the capacity of the individual's immune system to synthesize antibodies; the degree of protection desired; the severity of the condition being treated; the particular Env polypeptide selected and its mode of administration, among other factors. An appropriate effective amount can be readily determined by one of skill in the art. A "therapeutically effective amount" will fall in a relatively broad range that can be determined through routine trials.

Once formulated, the nucleic acid vaccines may be accomplished with or without viral vectors, as described above, by injection using either a conventional syringe or a gene gun, such as the Accell® gene delivery system (PowderJect Technologies, Inc., Oxford, England). Delivery of DNA into cells of the epidermis is particularly preferred as this mode of administration provides access to skin-associated lymphoid cells and provides for a transient presence of DNA in the recipient. Both nucleic acids and/or peptides can be injected either subcutaneously, epidermally, intradermally, intramucosally such as nasally, rectally and vaginally, intraperitoneally, intravenously, orally or intramuscularly. Other modes of administration include oral and pulmonary administration, suppositories, needle-less injection, transcutaneous and transdermal applications. Dosage treatment may be a single dose schedule or a multiple dose schedule. Administration of nucleic acids may also be combined with administration of peptides or other substances.

While the invention has been described in conjunction with the preferred specific embodiments thereof, it is to be understood that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

Experimental

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Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

EXAMPLE 1

A.1. Best-Fit and Homology Searches

The crystal structure of HXB-2 gp 120 was downloaded from the Brookhaven database (COMPLEX (HIV ENVELOPE PROTEIN/CD4/FAB) 15-JUN-98 1GC1 TITLE: HIV-1 GP120 CORE COMPLEXED WITH CD4 AND A NEUTRALIZING HUMAN ANTIBODY). Beta strands 3, 2, 21, and 20 of gp 120 form a sheet near the CD4 binding site. Strands β -3 and β -2 are connected by the V1/V2 loop. Strands β -21 and β -20 are connected by another small loop. The H-bonds at the interface between strands β -2 and β -21 are the only connection between domains of the "lower" half of the protein (joining helix alpha 1 to the CD4 binding site). This beta sheet and these loops mask some antigens (e.g., antigens which may generate neutralizing antibodies) that are only exposed during the CD4 binding.

Constructs that remove enough of the beta sheet to expose the antigens in the CD4 binding site, but leave enough of the protein to allow correct folding were designed. Specifically targeted were modifications to the small loop and, optional deletion of the V1/V2 loops. Three different types of constructs were designed: (1) constructs encoding polypeptides that leave the number of residues making up the entire 4-strand beta sheet intact, but replace one or more residues; (2) constructs that encode polypeptide having at least one residue of at least one beta strand excised or (3) constructs encoding polypeptides having at least two residues of at least one beta strand excised. Thus, a total of 6 different turns were needed to rejoin the ends of the strands.

Initially, residues in the small loop (residues 427-430, relative to HXB-2) and connected beta strands (β -20 and β -21) were modified to contain Gly and Pro (common in beta turns). These sequences were then used as the target to match in each search. The

geometry of the target was matched to known proteins in the Brookhaven Protein Data Bank. In particular, 5-residue turns (including an overlapping single residue at the N-terminal, the 2 residue target turn and 2 overlapping residues at the C-terminal) were searched in the databases. In other words, these modified loops add a 2 residue turn that should be able to support a geometry that will maintain the beta-sheet structure of the wild type protein. The calculations were performed using the default parameters in the Loop Search feature of the Biopolymer module of the Sybyl molecular modeling package. In each case, the 25 best fits based on geometry alone were reviewed and, of those, several selected for homology and fit.

In addition, it was also determined what modifications could be made to remove most of the V1/V2 loop (residues 124-198, relative to HXB-2) yet leave the geometry of the protein intact. As with the small loop, constructs were also designed which excised one or more residues from the β -2 strand (residues 119-123 of HXB-2), the β -3 strand (residues 199-201 of HXB-2) or both β -2 and β -3. For these constructs, known loops were searched to match the geometry of a pentamer (including two remaining residues from the N-terminal side, a 2 residue turn and 1 C-terminal residue). For these searches, Gly-Gly was preferred as the insert along with at least one C-terminal substitution.

A.2. Small Loop Replacements

In one aspect, the native sequence was replaced with residues that expose the CD4 binding site, but leave the overall geometry of the protein relatively unchanged. For the small loop replacements, the target to match was: ASN425-MET426-GLY427-GLY428-GLY431. Results of the search are summarized in Table 1.

Table 1: Search of Small Loop (Asn425 through Gly431)

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Rank	Sequence	RMSD	% Homology	Seq Id No.
Best fit	LYS-ASP-SER-ASN-ASN	0.16689	62.5	27
3	TYR-GLY-LEU-GLY-LEU	0.220308	62.5	28
4	GLU-ARG-GLU-ASP-GLY	0.241754	62.5	29
7	ARG-LYS-GLY-GLY-ASN	0.24881	100	30
12	TRP-THR-GLY-SER-TYR	0.26417	83.33	31

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Based on these results, constructs encoding Gly-Gly (#7), Gly-Ser (#12) or Gly-Gly-Asn (#7) were recommended.

As V1/V2 and one or more residues of β -2 and β -3 are also optionally deleted in the modified polypeptides of the invention, known loops to match the geometry of the V1/V2 loop were also searched. The V1/V2 loop the target to match was: Lys121-Leu-122-Gly123-Gly124-Ser199. Some notable matches are shown in Table 2:

Table 2: Search of V1/V2 loop (Lys121 through Ser199)

Rank	Sequence	RMSD	% Homology	Seq Id. No.
Best fit	GLN-VAL-HIS-ASP-GLU	0.154764	68.75	32
2	LYS-GLU-GLY-ASP-LYS	0.15718	81.25	33
9	ARG-SER-GLY-ARG-SER	0.173731	68.75	34
11	THR-LEU-GLY-ASN-SER	0.175554	81.25	35
16	HIS-PHE-GLY-ALA-GLY	0.178772	93.75	36

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Based on these searches, constructs encoding Gly-Asn in place of V1/V2 were recommended.

A.3. One Additional Residue Excisions

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For a slightly truncated small loop, one more residue was trimmed from each beta strand to slightly shorten the beta sheet. The target to match was: ILE424-ASN425-GLY426-GLY427-LYS432. Results are shown in Table 3:

Table 3: Search of Beta sheet shortened by One residue (Ile424 through Lys432)

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Rank	Sequence	RMSD	% Homology	Seq Id No.
Best fit:	ARG-MET-ALA-PRO-VAL	0.316805	58.33	37
Best	ASP-SER-ASP-GLY-PRO	0.440896	83.33	38
hom:				

Although these searches showed more variation and worse fits than the previous truncation, the Pro-Val or Pro-Leu encoding constructs were very similar. Accordingly, Ala-Pro encoding constructs were recommended.

Sequences encoding gp120 polypeptides having V1/V2 deleted and an additional residue from β -2 or β -3 excised were also searched. The V1/V2 loop the target to match was: VAL120-LYS121-GLY122-GLY123-VAL200. Some notable matches are shown in Table 4.

Table 4: Search of V1/V2 loop (Val120 through Val200)

Rank	Sequence	RMSD	% Homology	Seq Id No
Best fit:	THR-VAL-ASP-PRO-TYR	0.400892	58.33333	39
2	SER-THR-ASN-PRO-LEU	0.402575	54.16667	40
3	THR-ARG-SER-PRO-LEU	0.403965	58.33333	41
7	ARG-MET-ALA-PRO-VAL	0.440118	58.33333	42

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The construct encoding Ala-Pro (e.g., #7) was recommended.

A.4. Further Excisions

In yet another truncation, an additional residue was trimmed from the β -20 and β -21 strands to further shorten the beta sheet. The target to match was ILE423-ILE424-GLY425-GLY426-ALA433. Notable matches are shown in Table 5.

Table 5: Search of Beta sheet shortened by Two Residues (Ile423 through Ala433)

Rank	Sequence	RMSD	% Homology	Seq Id No
Best fit:	THR-TYR-GLU-GLY-VAL	0.130107	79.16666	43
2	GLN-VAL-GLY-ASN-THR	0.138245	79.16666	44
3:	THR-VAL-GLY-GLY-ILE	0.153362	100	45

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A construct encoding Gly-Gly (e.g., #3), which has 100% homology, was recommended.

Also searched were sequences encoding a deleted V1/V2 region and at least two residues excised from β -2, β -3 or at least one residue excised from β -2 and β -3. The target to match was: CYS119-VAL120-GLY121-GLY122-ILE201. Notable matches are shown in Table 6.

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Table 6: Search of V1/V2 loop (Cys119 through Ile201)

Rank	Sequence	RMSD	% Homology	Seq Id No
Best fit:	ASP-LEU-PRO-GLY-CYS	0.250501	75	46
4	ASP-VAL-GLY-GLY-LEU	0.290383	100	47

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It was determined that both constructs would be used.

B.1. Constructs encoding modified Env polypeptides

As described above, the native loops extruding from the 4- β antiparallel-stands were excised and replaced with 1 to 3 residue turns. The loops were replaced so as to leave the entire β -strands or excised by trimming one or more amino acid from each side of the connected strands. The ends of the strands were rejoined with turns that preserve the same backbone geometry (e.g., tertiary structure of β -20 and β -21), as determined by searching the Brookhaven Protein Data Bank.

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Table 7A is a summary of the truncations of the variable regions 1 and 2 recommended for this study, as determined in Example 1.A. above.

Table 7A

V1/V2 Modifications	SEQ ID NO	Figure
-LEU122-GLY-ASN-SER199	7	10
-LYS121-ALA-PRO-VAL200-	6	9
-VAL120-GLY-GLY-ILE201-	4	7
-VAL120- PRO-GLY- ILE201B-	5	8
-VAL120-GLY-ALA-GLY-ALA204-	3	6
-VAL120-GLY-GLY-ALA-THR202-	8	11
-VAL127-GLY-ALA-GLY-ASN195-	25	28

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As previously noted, the polypeptides encoded by the constructs of the present invention are numbered relative to HXB-2, but the particular amino acid residue of the polypeptides encoded by these exemplary constructs is based on SF-162. Thus, for example, although amino acid residue 195 in HXB-2 is a serine (S), constructs encoding polypeptides having then wild type SF162 sequence will have an asparagine (N) at this position. Table 7B shows just three of the variations in amino acid sequence between strains HXB-2 and SF162. The entire sequences, including differences in residue and amino acid number, of HXB-2 and SF162 are shown in the alignment of Figure 2 (SEQ ID NOs:1 and 2).

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Table 7B

HXB-2 amino acid number	HXB-2 Residue	SF162 Residue/amino acid number		
128	Serine (S)	Thr (T)/114		
195	Serine (S)	Asn (N)/188		
426	Met (M)	Arg (R)/411		

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Constructs containing deletions in the β -20 strand, β -21 stand and small loop were also constructed. Shown in Table 8 are constructs encoding truncations in these regions. The constructs in Table 8 are numbered relative to HXB-2 but the unmodified amino acid sequence is based on SF162. Thus, the construct encodes an arginine (Arg) as is found in

SF162 in the amino acid position numbered 426 relative to HXB-2 (See, also, Table 7B). Changes from wildtype (SF162) are shown in bold in Table 8B.

Table 8

Small Loop/ β -20 and β -21 (Modified) **SEQ ID NO** Figure -TRP427-GLY-GLY431-12 -ARG426-GLY-GLY-GLY431-10 13 14 -ARG426-GLY-SER-GLY431B-11 -ARG426-GLY-GLY-ASN-LYS432-12 15 -ASN425-ALA-PRO-LYS432-13 16 17 -ILE424-GLY-GLY-ALA433-14 -ILE423-GLY-GLY-MET434-15 18 GLN422-GLY-GLY-TYR435-19 16 17 20 -GLN422-ALA-PRO-TYR435B-

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The deletion constructs shown in Tables 7 and 8 for each one of the β-strands and combinations of them are constructed. These deletions will be tested in the Env forms gp120, gp140 and gp160 from different HIV strains like subtype B strains (e.g., SF162, US4, SF2), subtype E strains (e.g., CM235) and subtype C strains (e.g., AF110968 or AF110975).

20 Exemplary constructs for SF162 are shown in the

Figures and are summarized in Table 9. As noted above in Figure 2 and Table 7B, in the bridging sheet region, the amino acid sequence of SF162 differs from HXB-2 in that the Met426 of HXB-2 is an Arg in SF162. In Table 9, V1/V2 refers to deletions in the V1/V2 region; # bsm refers to a modification in the bridging sheet small loop.

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Table 9					
Construct	Seq. Id.	Fig.	Modification/Amino acid sequence		
Val120-Ala204	3	6	V1/V2: Val120-Gly-Ala-Gly-Ala204		
Val120-Ile201	4	7	V1/V2: Val120-Gly-Gly-Ile201		
Val120-Ile201B	5	8	V1/V2: Val120-Pro-Gly-Ile201		
Lys121-Val200	6	9	V1/V2: Lys121-Ala-Pro-Val200		

		T	able 9
Construct	Seq. Id.	Fig.	Modification/Amino acid sequence
Leu122-Ser199	7	10	V1/V2: Leu122-Gly-Asn-Ser199
Val120-Thr202	8	11	V1/V2: Val120-Gly-Gly-Ala-Thr202
Trp427-Gly431	9	12	bsm: Trp427-Gly-Gly431
Arg426-Gly431	10	13	bsm: Arg426-Gly-Gly-Gly431
Arg426-Gly431B	11	14	bsm: Arg426-Gly-Ser-Gly431
Arg426-Lys432	12	15	bsm: Arg426-Gly-Gly-Asn-Lys432
Asn425-Lys432	13	16	bsm: Asn425-Ala-Pro-Lys432
Ile424-Ala433	14	17	bsm: Ile424-Gly-Gly-Ala433
Ile423-Met434	15	18	bsm: Ile423-Gly-Gly-Met434
Gln422-Tyr435	16	19	bsm: Gln422-Gly-Gly-Tyr435
Val127-Asn195	25	28	bsm: Val127-Gly-Ala-Gly-Asn195
Gln422-Tyr435B	17	20	bsm: Gln422-Ala-Pro-Tyr435
Leu122-Ser199; Arg426-Gly431	18	21	V1/V2/bsm: Leu122-Gly-Asn-Ser199 Arg426 Gly-Gly-Gly431
Leu122-Ser199; Arg426-Lys432	19	22	V1/V2/bsm: Leu122-Gly-Asn-Ser199 Arg426 Gly-Gly-Asn-Lys432
Leu122-Ser199-Trp427- Gly431	20	23	V1/V2/bsm: Leu122-Gly-Asn-Ser199 Trp427 Gly-Gly431
Lys121-Val200- Asn425-Lys432	21	24	V1/V2/bsm: Lys121-Ala-Pro-Val200 Asn425 Ala-Pro-Lys432
Val120-Ile201-Ile424- Ala433	22	25	V1/V2/bsm: Val120-Gly-Gly-Ile201 Ile424-Gly-Gly-Ala433
Val120-Ile201B-Ile424- Ala433	23	26	V1/V2/bsm: Val120-Pro-Gly-Ile201 Ile424-Gly-Gly-Ala43
Val120-Thr202; Ile424- Ala433	24	27	V1/V2/bsm: Val120-Gly-Gly-Ala-Thr202 Ile424-Gly-Gly-Ala433
Val127-Asn195; Arg426-Gly431	25	29	V1/V2/bsm: Val127-Gly-Ala-Gly-Asn195 Arg426-Gly-Gly-Gly431

Combinations of V1/V2 deletions and bridging sheet small loop modifications in addition to those specifically shown in Table 9 are also within the scope of the present invention. Various forms of the different embodiments of the invention, described herein, may be combined.

The first screening will be done after transient expression in COS-7, RD and/or 293 cells. The proteins that are expressed will be analyzed by immunoblot, ELISA, and for binding to mAbs directed to the CD4 binding site and other important epitopes on gp120 to determine integrity of structure. They will also be tested in a CD4 binding assay and, in addition, the binding of neutralizing antibodies, for example using patient sera or mAb 448D (directed to Glu370 and Tyr384, a region of the CD4 binding groove that is not altered by the deletions).

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The immunogenicity of these novel Env glycoproteins will be tested in rodents and primates. The structures will be administered as DNA vaccines or adjuvanted protein vaccines or in combined modalities. The goal of these vaccinations will be to archive broadly reactive neutralizing antibody responses.

Claims:

What is claimed is:

- 1. A polynucleotide encoding a modified HIV Env polypeptide wherein the polypeptide has at least one amino acid deleted or replaced in the region corresponding to residues 420 to 436 relative to HXB-2 (SEQ ID NO:1).
- 2. The polynucleotide of claim 1, wherein the region corresponding to residues 124198 relative to HXB-2 is deleted and at least one amino acid is deleted or replaced in the regions corresponding to the residues 119 to 123 and 199 to 210 relative to HXB-2 (SEQ ID NO:1).
- 3. The polynucleotide of claim 1, wherein at least one amino acid in the region corresponding to residues 427 through 429 relative to HXB-2 (SEQ ID NO:1) is deleted or replaced.
 - 4. The polynucleotide of claim 2, wherein at least one amino acid of the in the region corresponding to residues 427 through 429 relative to HXB-2 (SEQ ID NO:1) is deleted or replaced.
 - 5. The polynucleotide of claim 1, wherein the amino acid sequence of the modified HIV Env polypeptide is based on strain SF162.
- 6. An immunogenic modified HIV Env polypeptide having at least one amino acid deleted or replaced in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO:1).
- 7. The polypeptide of claim 6, wherein one amino acid is deleted in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO:1).

8. The polypeptide of claim 6, wherein more than one amino acid is deleted in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO:1).

- 9. The polypeptide of claim 6, wherein at least one amino acid is replaced in the region corresponding to residues 420 through 436, relative to HXB-2 (SEQ ID NO:1).
 - 10. The polypeptide of claim 6, wherein at least one amino acid residue between about amino acid residue 427 and amino acid residue 429 relative to HXB-2 (SEQ ID NO:1) is deleted or replaced.

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11. The polypeptide of claim 6, wherein the V1 and V2 regions of the polypeptide are

truncated.

- 12. The polypeptide of claim 10, wherein the V1 and V2 regions of the polypeptide are truncated.
 - 13. The polypeptide of claim 6, wherein the amino acid sequence of the modified HIV Env polypeptide is based on strain SF162.
- 20 14. A construct comprising the nucleotide sequence depicted in Figure 6 (SEQ ID NO:3).
 - 15. A construct comprising the nucleotide sequence depicted in Figure 7 (SEQ ID NO:4).
 - 16. A construct comprising the nucleotide sequence depicted in Figure 8 (SEQ ID NO:5).
- 17. A construct comprising the nucleotide sequence depicted in Figure 9 (SEQ ID30 NO:6).

18. A construct comprising the nucleotide sequence depicted in Figure 10 (SEQ ID NO:7).

- 19. A construct comprising the nucleotide sequence depicted in Figure 11 (SEQ ID5 NO:8).
 - 20. A construct comprising the nucleotide sequence depicted in Figure 12 (SEQ ID NO:9).
- 10 21. A construct comprising the nucleotide sequence depicted in Figure 13 (SEQ ID NO:10).
 - 22. A construct comprising the nucleotide sequence depicted in Figure 14 (SEQ ID NO:11).
 - 23. A construct comprising the nucleotide sequence depicted in Figure 15 (SEQ ID NO:12).
- 24. A construct comprising the nucleotide sequence depicted in Figure 16 (SEQ ID NO:13).

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- 25. A construct comprising the nucleotide sequence depicted in Figure 17 (SEQ ID NO:14).
- 26. A construct comprising the nucleotide sequence depicted in Figure 18 (SEQ ID NO:15).
 - 27. A construct comprising the nucleotide sequence depicted in Figure 19 (SEQ ID NO:16).
 - 28. A construct comprising the nucleotide sequence depicted in Figure 20 (SEQ ID NO:17).

29. A construct comprising the nucleotide sequence depicted in Figure 21 (SEQ ID NO:18).

- 30. A construct comprising the nucleotide sequence depicted in Figure 22 (SEQ IDNO:19).
 - 31. A construct comprising the nucleotide sequence depicted in Figure 23 (SEQ ID NO:20).
- 32. A construct comprising the nucleotide sequence depicted in Figure 24 (SEQ ID NO:21).
 - 33. A construct comprising the nucleotide sequence depicted in Figure 25 (SEQ ID NO:22).
 - 34. A construct comprising the nucleotide sequence depicted in Figure 26 (SEQ ID NO:23).
- 35. A construct comprising the nucleotide sequence depicted in Figure 27 (SEQ ID NO:24).

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- 36. A construct comprising the nucleotide sequence depicted in Figure 28 (SEQ ID NO:25).
- 37. A construct comprising the nucleotide sequence depicted in Figure 29 (SEQ ID NO:26).
 - 38. A vaccine composition comprising a polynucleotide encoding a modified Env polypeptide according to any one of claims 1-5.
 - 39. A vaccine composition comprising a polynucleotide construct encoding a modified Env polypeptide according to any of claims 14-37.

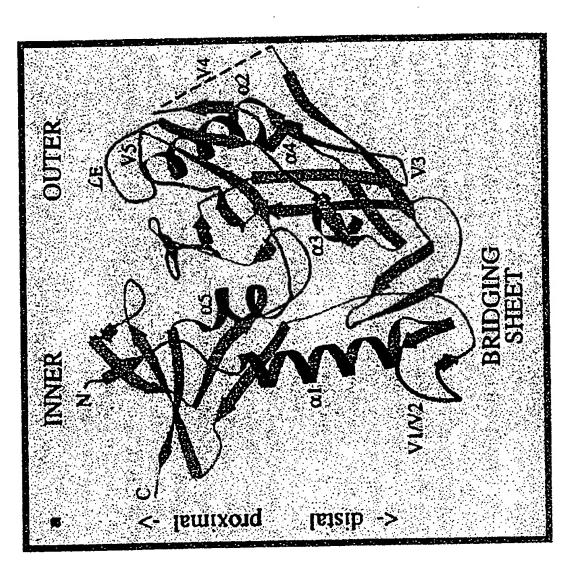
40. A vaccine composition comprising a modified Env polypeptide according to any of claims 6-13.

41. The vaccine composition of any of claims 38-40, further comprising an adjuvant.

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- 42. A method of inducing an immune response in subject comprising, administering a polynucleotide according to any one of claims 1-5 in an amount sufficient to induce an immune response in the subject.
- 43. A method of inducing an immune response in subject comprising, administering a polynucleotide construct according to any one of claims 14-37 in an amount sufficient to induce an immune response in the subject.
- 44. A method of inducing an immune response in a subject comprising administering a composition comprising a modified Env polypeptide according to any one of claims 6-13, wherein the composition is administered in an amount sufficient to induce an immune response in the subject
- 45. The method of any of claims 42-44 further comprising administering an adjuvant to the subject.
 - 46. A method of inducing an immune response in a subject comprising
 - (a) administering a first composition comprising a polynucleotide according to any of claims 1-5 in a priming step and
 - (b) administering a second composition comprising a modified Env polypeptide according to any of claims 6-13, as a booster, in an amount sufficient to induce an immune response in the subject.
- 47. The method of claim 46 wherein the first composition or second composition further comprise an adjuvant.

48. The method of claim 46 wherein the first and second compositions further comprise an adjuvant.



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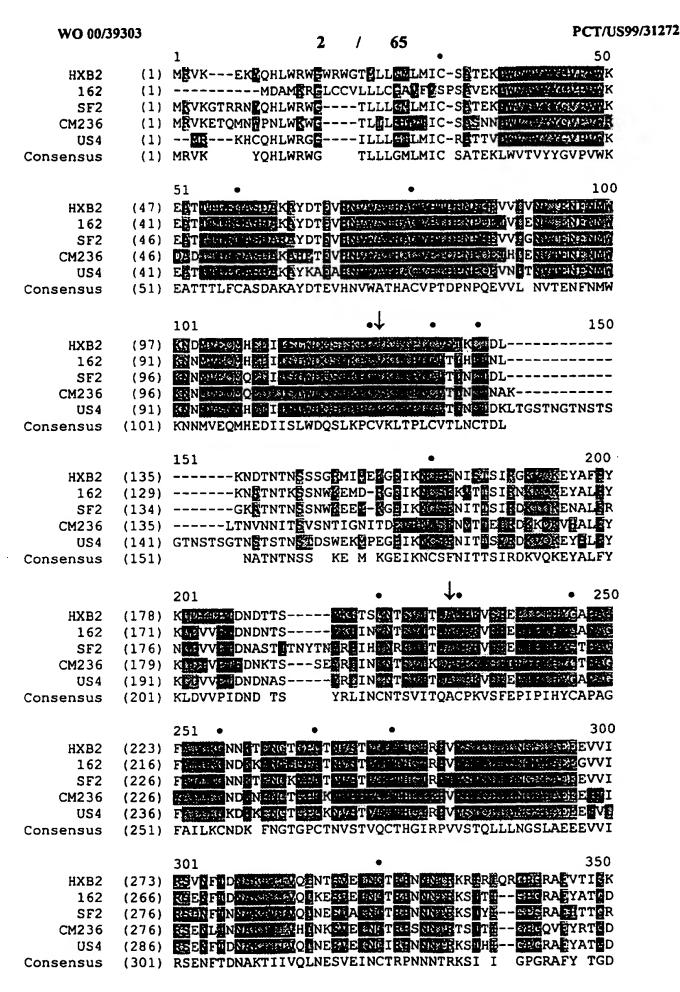


FIG. 2A

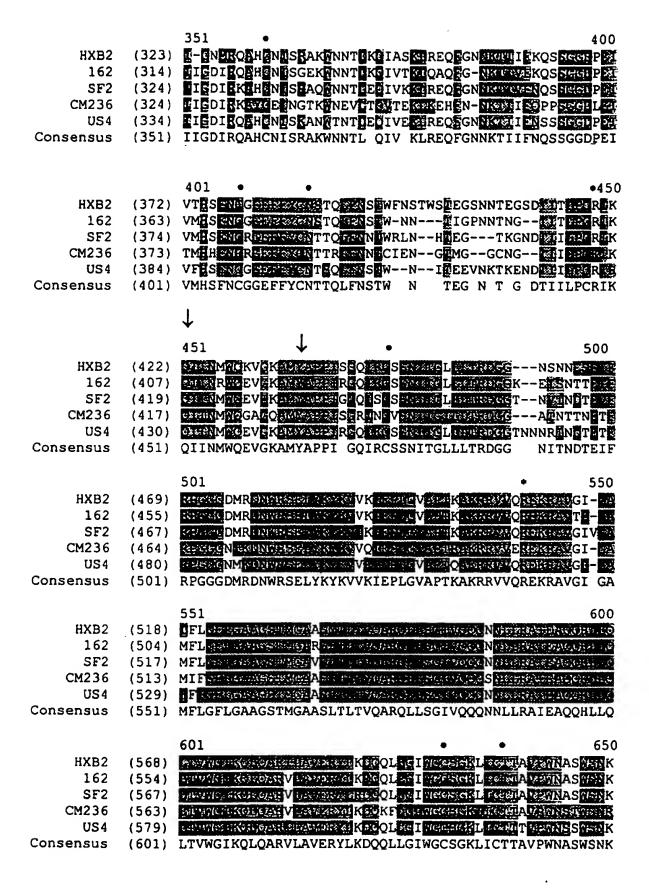


FIG. 2B

PCT/US99/31272

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FIG. 2C

WO 00/39303		10	,	65	PC	T/US99/31272
Val120-Thr202	/1199		しょう かかがあって		GTGGCCCCCACCAA	
Lys121-Val200	(1205)				GTGGCCCCCACCAA	
Consensus	(1241)				GTGGCCCCCACCAA	
Collsensus	(1241)	1281	COAGC	.ccc1666c	1320	
Tau 122 Cam 100	/10511		acmoics	CONCOCO		
Leu122-Ser199	(1251)				AGAAGCGCGCCGTG	
Val127-Asn195	(1281)	in the time that the many of a second of	-		AGAAGCGCGCCGTG	
Val120-Ile201B	(1239)				AGAAGCGCGCCGTG	
Val120-Ala204	(1233)	the state of the s			AGAAGCGCGCCGTG	
Val120-Ile201	(1239)				ÄĜAAGCGCGCCGTG	
Val120-Thr202	(1239)				AGAAGCGCGCCGTG	
Lys121-Val200	(1245)				AGAAGCGCGCCGTG	
Consensus	(1281)		CGTGGT	GCAGCGCG	AGAAGCGCGCCGTG	
		1321		N	1360	
Leul22-Ser199	(1291)	14 berg 1 from 11 2 0 000 1 000 000 1 1 1 1 1 1 1 1 1			CCTGGGGGGCGCCG	
Val127-Asn195	(1321)	r*		process of annual to the	CCTGGGCGCCGCCG	
Val120-Ile201B	(1279)				CCTGGGGGCCCCC	
Val120-Ala204	(1273)	1 a Tail ball 1 a Mark ball and the desired the state of the transfer of the t			CCTGGGCGCCGCCG	
Val120-Ile201	(1279)				CCTGGGCGCCGCCG	
Val120-Thr202	(1279)		101,011		CCTGGGCGCCGCCG	
Lys121-Va1200	(1285)			A	CCTGGGCGCCGCCG	
Consensus	(1321)	ACCCTGGGCGCCA	TGTTC	CTGGGCTT	CCTGGGCGCCGCCG	
		1361			1400	
Leu122-Ser199	(1331)				ACCCTGACCGTGCA	
Val127-Asn195	(1361)				ACCCTGACCGTGCA	
Val120-Ile201B	(1319)	· · · · I			ACCCIGACCGTGCA	
Val120-Ala204	(1313)				ACCCTGACCGTGCA	
Val120-Ile201	(1319)	GCAGCACCATEGG	CGECC	GEAGGETG	ACCCTGACCGTGCA	
Val120-Thr202	(1319)	GCAGCACCATEGG	CGCCC	GCAGCCTG.	ACCCTGACCGTGCA	
Lys121-Val200	(1325)	GCAGCACCATGGG	CGCCC	GCAGCCTG	ACCCTGACCGTGCA	
Consensus	(1361)	GCAGCACCATGGG	CGCCC	GCAGCCTG	ACCCTGACCGTGCA	
		1401			1440	
Leul22-Ser199	(1371)				TGCAGCAGCAGAAC	•
Val127-Asn195	(1401)	GGCCCGCCAGCTG	CTGAG	CGGCATCG	TGCAGCAGCAGAAC	
Val120-Ile201B	(1359)				IGCAGCAGCAGAAC	
Val120-Ala204	(1353)	GGCCGCCAGCTG	CTGAG	CGGCATCG	rgeageageagaac	
Val120-Ile201	(1359)	GGCCCGCCAGGTG	CECAG	egggateg	IGCAGCAGCAGAAC	
Val120-Thr202	(1359)	GGCCCGCCAGCTC	CHGAG	eggerveg	PGCAGCAGCAGAAC	
Lys121-Val200	(1365)	GGCCCGCCAGCTG	CTGAG	CGGCATCG'	rgcagcagcagaac	
Consensus	(1401)	GGCCCGCCAGCTG	CTGAG	CGGCATCG	TGCAGCAGCAGAAC	
		1441			1480	
Leu122-Ser199	(1411)	AACCTGCTGCGCG	CCATC	GAGGCCCA	CAGCACCTGCTGC	
Val127-Asn195	(1441)				CAGCACCTGCTGC	
Val120-Ile201B	(1399)				CAGCACCTGCTGC	
Val120-Ala204	(1393)	AACCHGG IGG G	CATC	GAGGGCCA	CAGCACCTGCTGC	
Val120-Ile201	(1399)	AMCONGONGOGC	CATC	SAGGECCA	CAGCACCTGCTGC	
Val120-Thr202	(1399)	AACCTGCTGCGCG	CATC	AGGECCAY	CAGCACCTGCTGC	
Lys121-Val200	(1405)	AACCTGCTGCGCG	CATC	SAGGECCAC	CAGCACCTGCTGC	
Consensus	(1441)	AACCTGCTGCGCGC	CCATC	SAGGCCCAC	CAGCACCTGCTGC	
		1481			1520	
Leu122-Ser199	(1451)	AGCTGACCGTGTG	GGCA1	CAAGCAGC	TGCAGGCCCGCGT	
Val127-Asn195	(1481)	AGCTGACCGTGTG				
Val120-Ile201B	(1439)	AGCTGACCGTGTG	GGCAT	CAAGCAGC	TGCAGGCCCGCGT	
Val120-Ala204	(1433)	AGCTGACCGTGTG		The same of the sa	rest p page page r	
Val120-Ile201	(1439)	AGCTGACCGTGTG		The state of the s		
Val120-Thr202	(1439)	AGCTGACCGTGTG			and the second s	
Lys121-Va1200	(1445)	AGCTGACCGTGTG				
Consensus	(1481)	AGCTGACCGTGTGG			•	
	- •					

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1521
                 (1491) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
 Leul22-Ser199
                 (1521) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
 Val127-Asn195
                 (1479) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
Val120-Ile201B
                 (1473) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
 Val120-Ala204
                 (1479) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
 Val120-Ile201
                 (1479) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
 Val120-Thr202
                 (1485) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
 Lys121-Val200
                 (1521) GCTGGCCGTGGAGCGCTACCTGAAGGACCAGCAGCTGCTG
     Consensus
                         1561
                                                              1600
                 (1531) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
 Leul22-Ser199
                 (1561) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG (1519) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
 Val127-Asn195
Val120-Ile201B
 Val120-Ala204
                 (1513) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
                 (1519) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
 Val120-Ile201
                (1519) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
 Val120-Thr202
                (1525) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
 Lys121-Val200
                (1561) GGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCACCG
     Consensus
                 (1571) CCGTGCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
 Leu122-Ser199
 Val127-Asn195
                (1601) CCGTGCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
                (1559) CCGTGCCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
Val120-Ile201B
                 (1553) CCGTGCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
 Val120-Ala204
                 (1559) CCGTGCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
 Val120-Ile201
                (1559) CCGTGCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
 Val120-Thr202
                (1565) CCGTGCCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
 Lys121-Va1200
                 (1601) CCGTGCCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGA
     Consensus
                        1641
                 (1611) CCAGATCTGGAACAACATGACCTGGATGGAGTGGGAGCGC
 Leu122-Ser199
                (1641) CCAGATCTGGAACAACATGACCTGGATGGAGTGGGAGCGC
 Val127-Asn195
                (1599) CCAGATCTGGAACAACATGACCTGGATGGAGTGGAGCGC (1593) CCACATCTGGAAGAACATGACCTGGATGGAGTGGAACGCCC
Val120-Ile201B
 Val120-Ala204
                 (1599) CCAGATCTGGAAGAACATGACCTGGATGGAGTGGGAGGGC
 Val120-Ile201
                 (1599) CCAGATCTGGAACAACATGAGGTGGAAGGGGGGGGGGGCGC
 Val120-Thr202
                (1605) CCAGATCTGGAACAACATGACCTGGATGGAGTGGGAGCGC
 Lys121-Val200
                (1641) CCAGATCTGGAACAACATGACCTGGATGGAGTGGGAGCGC
     Consensus
                (1651) GAGATCGACAACTACACCAACCTGATCTACACCCTGATCG
Leu122-Ser199
                (1681) GAGATEGACAACTACACCAACCTGATCTACACCCTGATCG
 Val127-Asn195
                (1639) GAGATEGACAACTACACCAACCTGATCTACACCCTGATCG
Val120-Ile201B
Val120-Ala204
                (1633) GAGATICGACAACTVACACCAACGTGATOTACACCCTGATCG
                        GAGATUGAGAAGTACACCAACCTGATCTAGACCCTGATCG
 Val120-Ile201
                (1639)
                        GAGATICGACIACIACACCAACCTCATETACACCCTGATICG
Val120-Thr202
                (1639)
 Lys121-Val200
                (1645)
                       GAGATCGACAACTACACCAACCTGATCTACACCCTGATCG
                (1681) GAGATCGACAACTACACCAACCTGATCTACACCCTGATCG
     Consensus
                (1691) AGGAGAGCCAGAACCAGCAGGAGAACGAGCAGGAGCT
Leu122-Ser199
                (1721) AGGAGAGCCAGAACCAGCAGGAGAAGAACGAGCAGGAGCT
Val127-Asn195
                (1679) AGGAGAGCCAGAACCAGCAGGAGAAGAACGAGCAGGAGCT
Val120-Ile201B
                (1673) AGGAGACCAGAACCAGCAGGAGAAGAACGAGCAGGAGCT
Val120-Ala204
                (1679) AGGAGAGCCAGAACCAGCAGGAGAAGAACGAGCAGCAGCT
Val120-Ile201
                (1679) AGGAGAGCCAGAACCAGCAGGAGAAGAACGAGCAGGAGCT
Val120-Thr202
                (1685) AGGAGAGCCAGAACCAGCAGGAGAACGAGCAGGAGCT
Lys121-Val200
                (1721) AGGAGAGCCAGAACCAGCAGGAGAACGAGCAGGAGCT
     Consensus
                (1731) GCTGGAGCTGGACAAGTGGGCCAGCCTGTGGAACTGGTTC
Leu122-Ser199
                (1761) GCTGGAGCTGGACAAGTGGGCCAGCCTGTGGAACTGGTTC
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Val120-Thr202
                                           (1959) CGACCGCGACCGCAGCAGCCCCCTGGTGCACGGCCTGCTG
                                            (1965) CGACCGCGACCGCAGCAGCCCCTTGGTGCACGGCCTGCTG
     Lys121-Val200
                Consensus
                                              (2001) CGACCGCGACCGCAGCAGCCCCCTGGTGCACGGCCTGCTG
                                            (2011) GCCCTGATCTGGGACGACCTGCGGAGCCTGTGCCTGTTCA
     Leu122-Ser199
                                            (2041) GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCA
     Val127-Asn195
  Vall20-Ile201B (1999) GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCA
     Val120-Ala204
                                            (1993) GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCA
     Val120-Ile201
                                             (1999) GCCCTGATCIGGGACGACCTGCGCAGCCTGTGCCTGTTCA
                                            (1999) GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCA
    Val120-Thr202
                                             (2005) GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCA
    Lys121-Val200
                                             (2041) GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCA
                Consensus
                                                                 2081
    Leu122-Ser199
                                             (2051) GCTACCACCGCCTGCGCGACCTGATCCTGATCGCCGCCCG
    Val127-Asn195 (2081) GCTACCACEGCCTGCGCGACCTGATCCTGATCGCCGCCG
  Vall20-Ile201B (2039) GCTASCACEGCCTGGCCGACCTGATECTGATCGCCGCCGC Vall20-Ala204 (2033) GCTASCACCGCCTGGGCGACCTGATCCTGATCGCCGCCGG
    Val120-Ile201
                                             (2039) GCTACCACGGCTGCGCGAGCTGATCCTGATCGCCGCCGG
    Val120-Thr202
                                             (2039) GCTASCACGGCCTECGCGACCTGATCCTGATCGCCGCCCG
                                            (2045) GCTACCACGGCCTGCGCGACCTGATCCTGATCGCCGCCCG
    Lys121-Val200
               Consensus
                                            (2081) GCTACCACCGCCTGCGCGACCTGATCCTGATCGCCGCCCG
                                           (2091) CATCC ISCARCIFICATEGGCCGCGCGGGCTGGGAGGCCCTG
    Leu122-Ser199
    Val127-Asn195
                                        (2079) CATCCTGGAGCTGCTGGGCCGCGGGGGGGGCCCTG
(2073) CATCCTGGAGCTGCTGGGCGCGCGGGGGGGCCCTG
(2079) CATCCTGGAGCTGCTGGGCGGCGGGGGGGGCCCTG
(2079) CATCCTGGAGCTGCTGGGCGGCGGGGGGGGCCCTG
(2085) CATCGTGGAGCTGCTGGGCCGCGGGGGGGGCCCTG
 Val120-Ile201B
    Val120-Ala204
   Val120-Ile201
    Val120-Thr202
   Lys121-Val200
              Consensus
                                           (2121) CATCGTGGAGCTGCTGGGCCGCCGCGGCTGGGAGGCCCTG
                                           (2131) NACYAGREECE A CONCENCIA CHACT GEAR COAGGAGC (2161) NACHACT GEGENACO (GERCACT ACT GEAR COAGGAGC (2119) NACTACT GEORGESCAN COAGGAGC GEART ACT GEAR COAGGAGC
   Leul22-Ser199
                                         (2131)
   Val127-Asn195
Val120-Ile201B
                                          (2119)
                                          (2113) वित्रवारी सम्बद्धां वर्षा सम्बद्धाः वर्षा वरम वर्षा वरम वर्षा वर्
   Val120-Ala204
   Val120-Ile201
                                         (2119) Programmer and Construction and Construction (2119)
                                        (2119) AAGWAGWEGEGEANGEWEGWEGAGWAGWAGGAGC
(2125) AAGWAGWEGEGEGAWWONGEWEGAGWAGWAGGAGC
  Val120-Thr202
  Lys121-Val200
             Consensus
                                          (2161) AAGTACTGGGGCAACCTGCTGCAGTACTGGATCCAGGAGC
                                                               2201
                                                             ŊĠŊŊĠŊŊĠŊĠĠĠĠĠŖĠŊĠŶĸŊĠĸĸŊĠĠŊĠĠĠŊŢĊĠĊĊŊŢ
  Leu122-Ser199
                                           (2171)
  Val127-Asn195
                                           (2201) WEAREN ASTERS OF SEASON REPORTED ASSESSMENT COCCAT
                                                             HEIMAGENAUTCEGOCERCE (Cocare alexa de Vale e est pre Go de A
Val120-Ile201B
                                           (2159)
                                                             Val120-Ala204
                                          (2153)
                                         (2159) REMARKACKEESCUSKEREESCUSKEESKEECKECKTEGECKT
  Val120-Ile201
  Val120-Thr202
                                          (2159) WENTERNAME OF SECULOR S
                                          (2165) TGAAGAACAGCGCGTGAGCCTGTTCGACGCCATCGCCAT
  Lys121-Val200
                                          (2201) TGAAGAACAGCGCCGTGAGCCTGTTCGACGCCATCGCCAT
             Consensus
                                                              2241
                                          (2211) CGCCGTGGCCGAGGGCACCGACCGCATCATCGAGGTGGCC
 Leul22-Ser199
                                          (2241) CGCCCTGGCCGAGCGCACCGACCGCATCATCGAGGTGGCC
  Val127-Asn195
                                         (2199) CGCCETEGCCEAGEGCACCGACCECATCATCGAGGTGGCC (2193) CGCCETEGCCGAGGGCACCGACCGCATCATCGAGGTGGCC (2199) CGCCETEGCCGAGGGCACCGACCGCCATCATCGAGGTGGCC
Val120-Ile201B
  Val120-Ala204
  Val120-Ile201
                                        (2199) CGCCGTGCCGAGGGGACCGACCGCATCATCGAGGTGGCC
 Val120-Thr202
 Lys121-Val200
                                        (2205) CGCCGTGGCCGAGGGCACCGACCGCATCATCGAGGTGGCC
                                      (2241) CGCCGTGGCCGAGGGCACCGACCGCATCATCGAGGTGGCC
            Consensus
```

		2281	2320
Leu122-Ser199	(2251)	CAGCGCATCGGCCGCCCTTCCTGCA	CATCCCCCGCCGCA
Val127-Asn195	(2281)	CAGCGCATCGGCCGCGCCTTCCTGGA	CATECCCCGCCGCA
Val120-Ile201B	(2239)	CAGCGCATCGGCGCGCCCTTCCTGCA	CATCCCCCCCCCCA
Val120-Ala204	(2233)	CAGCGCATCGGCCGCCCTTCCTGCA	CATCCCCCCCCCCA
Val120-Ile201	(2239)	CAGCGCATCGGCCGCGCCTTCCTGCA	CATCCCCCGCCGCA
Val120-Thr202	(2239)	CAGCGCATCGGCCGCGCCTTCCTGCA	CATCCCCCGCCGCA
Lys121-Val200	(2245)	CAGCGCATCGGCCGCCCTTCCTGCA	CATCCCCCCCCCCA
Consensus	(2281)	CAGCGCATCGGCCGCGCCTTCCTGCA	CATCCCCCGCCGCA
		2321	2360
Leul22-Serl99	(2291)	TCCGCCAGGGCTTCGAGCGCGCCCTG	Company and the second
Val127-Asn195	(2321)	TCCGCCAGGGCTTCGAGCGCGCCCTG	parally area of their graph is highly marks with the
Val120-Ile201B	(2279)	TCCGCCAGGGCTTCGAGCGCGCGTG	
Val120-Ala204	(2273)	Tecceenced	
Val120-Ile201	(2279)	TCCCCCAGGCCTTCGAGCGCGCCCTG	
Val120-Thr202	(2279)	TCCGCCAGGGCTTCGAGCGCGCGCTG	4
Lys121-Val200	(2285)	TCCGCCAGGGCTTCGAGCGCGCCCTG	CTGTAACTCGAGCG
Consensus	(2321)	TCCGCCAGGGCTTCGAGCGCCCCTG	CTGTAACTCGAG
		2361	
Leu122-Ser199	(2331)	TGCT	
Val127-Asn195	(2359)		
Vall20-Ile201B	(2319)	TGCT	
Val120-Ala204	(2311)		
Val120-Ile201	(2317)		
Val120-Thr202	(2317)	we 40 to 40	
Lys121-Va1200	(2325)	TGCT	
Consensus	(2361)		

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Ile424-Ala433	(1)	कार्यकार्या व्यक्तिक	steteler	(cletit)	rolejava rena	अंदर्शास्त्रक्षात्त्रस्थात्। इ.स.च्या	SEPTIME OF
Trp427-Gly431	(1)					gererate escience	
Gln422-Tyr435B	(1)					Acthematicieleiki	
Arg426-Gly431	(1)					ील्यास्त्रीशासिस्टार	
Ile423-Met434	(1)					संदर्भारत् <i>राज्यानु</i> हो अर्थ	
Gln422-Tyr435	(1)					Agadynoligeisus	
Arg426-Lys432	(1)		_			शकार्यक्षेत्रहास्टान्स्य स्टब्स्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट्रिक्ट	
Arg426-Gly431B	(1)					त्तराज्यकोष्ट्री स्ट िस्	
Asn425-Lys432	(1)					नवर्गे हुं इस्ति होता है। इस्ति इस्ति होता है।	
Consensus	(1)					AGAGAGGGCT	
		41					80
Ile424-Ala433	(41)					<i>∾र्मा स</i> न्त्रसम्बद्धाः	
Trp427-Gly431	(41)	The second secon				लुक्त्रसंदर्भागिकेषुत्रस्	
Gln422-Tyr435B	(41)					हेशसंत्रकाटशियामुङ्का <u>ल्</u>	
Arg426-Gly431	(41)			-		र भीतिक स्टब्स्स्ट्रिकास्ट्र	
Ile423-Met434	(41)					1.16 A S S S S S S S S S S S S S S S S S S	
Gln422-Tyr435	(41)	देख, द्रमुख दोदा, सद्या म					
Arg426-Lys432	(41)	स्वर्थका स्थापन अस्तर्भ					
Arg426-Gly431B	(41)	SAF EN HELC HARLOS.		-	the state of the s	the state of the s	
Asn425-Lys432	(41)				THE RESERVE TO THE PERSON NAMED IN COLUMN TWO IS NOT THE PERSON NAMED IN COLUMN TWO IS NAME	એના કૃતિનો સામા હોલી <mark>છે</mark>	
Consensus	(41)	GTGTGCTGCT 81	GCTG	TGTG	GAGCAGT	CTTCGTTTCGC	CCCAG 120
Ile424-Ala433	(81)	र्वत्र रहेग हरेग	William.	· jegite	etal dine	इ.स.च्याम (१.४१) श्लीली	
Trp427-Gly431	(81)					क्षाप्तान् कृति। जन्म	
Gln422-Tyr435B	(81)	The same of the sa				Carried Soft Bring Tar CAR	
Arg426-Gly431	(81)	अंदर्भा द्वादा १ हरू दर्भ ४ क					
Ile423-Met434	(81)	शेल्ट (साम्भारतस्य स्ट)					
Gln422-Tyr435	(81)	खेलुक स्टब्स्पटका ल	than jey	क्षत्री प्रदेश	ettire ti estipor	પ્લુકે ઉપયુર્વ વર્ષો કે હવે છે. પ્લુકે ઉપયુર્વ વર્ષો કે હવે છે.	€ /८, इ€
Arg426-Lys432	(81)	अंद्रांश नाराम साहेगांन	1.10%	**C-141C	elepreparag	अहेत. अहारा केन्द्रसंस्थानक	Mon Ke
Arg426-Gly431B	(81)	क्षेत्रका विश्वविद्या है।	MAGE.	vévre	Schilling)	spainted, thricks	lelerie
Asn425-Lys432	(81)	बाल्क बाल्क्ष्रस्थानाम्	er June	भूक्षभूष्ट	(देशकाद्योग्स्ट(क)	क्षांग्रह्मा <mark>स्ट्रास्ट्रास्ट्रस्टस्ट्र</mark>	एक ए
Consensus	(81)	CGCCGTGGAG	AAGC'	TGTG	GGTGACC	GTGTACTACGG	GCGTG 160
Ile424-Ala433	(121)	ल्लास्य । स्ट्रेक्स स्ट्र क	36133	#Krio	State State Colors	र्व - द्रोन्स्ट्रस्थ्रिस्ट्रस्य स्ट्रिस्ट्	
Trp427-Gly431	(121)	संस्थातिक स्थापिक					
Gln422-Tyr435B	(121)	viere andoverere			The second second		
Arg426-Gly431	(121)	१८ विकास स्थापन स्थापन		- Address of the State of the S		***	
Ile423-Met434	(121)	अर्थान कुरसंक्रमां क् <mark>रस्त</mark> ्रीहरू					
Gln422-Tyr435	(121)	र्नेश्व श्रामक्ष्यं वृक्ष				AND DESCRIPTION OF THE PARTY OF	
Arg426-Lys432	(121)	CONTRACTOR CAST			-		
Arg426-Gly431B	(121)	स्वतः ।कन्युत्रस् व देश					
Asn425-Lys432	(121)	संस्ता १० एर वेहारा					
Consensus	(121)	CCCGTGTGGA	AGGA	GGCC.	ACCACCA	CCTGTTCTGC	
Ile424-Ala433	(161)	161 सन्तर्भागास्त्रास्ट्रा	deser	3-18-57	os, envelocible	h interpresentation	200
Trp427-Gly431	(161)	#, £, \$ 1510, LE [6] (17) A15					
Gln422-Tyr435B	(161)	and the spirit of the state of				THE RESERVE AND DESCRIPTION OF THE PERSON OF	
Arg426-Gly431	(161)	ricial stricture (univit					
Ile423-Met434	(161)	stronger, etclispelegre					-
Gln422-Tyr435	(161)	ejs tegans (eine start)					
Arg426-Lys432	(161)	rickstifeleleie htt					The state of the s
Arg426-Gly431B	(161)	শ্রু লেট্ড প্রতি দেই ১৯৮					
Asn425-Lys432	(161)	eletelyteleteletikile					
Consensus	(161)	GCGACGCCAA					TGTG
Ile424-Ala433	(201)	201 রলগলনার্মন্তর্	(Say	الرة: ال	eleiciennetej	ગુરાલી છે. આ માનું જોવા છે. મુખ્યા <mark>માનું પ્રાથમિક પ્રાથમિક</mark>	240 (GCAG
				.,	-1-27		

FIG. 4A

WO 00/39303		16 /	65	PCT/US99/31272
Trp427-Gly431	(201)	श्रुवति । । । । । । । । । । । । । । । । । । ।	Petalaianscretoria ul	ologia exceptional
Gln422-Tyr435B	(201)	संस्थात अस्ति। इस्तिस्थान्य वर्षाः		
Arg426-Gly431	(201)	असीर दश्यामान्य होता त्यापार है		
Ile423-Met434	(201)	स्वतंत्रं प्रदेशके क्षेत्रं क्षेत्रं के स्वतंत्रं के स्वतंत्रं		
Gln422-Tyr435	(201)	डीयाद्यद्वभागीहर्भित्रीयद्वातात्र्वेत्राद्		
Arg426-Lys432	(201)	्रिटोब्राचरक्षान्य क्रिक्टब्राच्या क्रिक्टब्राह्		
Arg426-Gly431B	(201)	द्वासहार महाराज्यात स्थान		
Asn425-Lys432	(201)	deteletikojojojustajelentetrika		
Consensus	(201)	GGCCACCCACGCCTGCG		
		241		280
Ile424-Ala433	(241)	est/essancicantications/state		
Trp427-Gly431	(241)	देशकान्यस्दर्भः विशेषकार्यस्तिवर्षकार्यस्		
Gln422-Tyr435B	(241)	क्षरेत्वकृत्यस्य स्टिप्स्यास्य प्रस्तिकार्यं व्यवस्था		
Arg426-Gly431	(241)	देशीरका महास्तितम्बद्धान्त्रीयाम् स्वार्		
Ile423-Met434	(241)	द्रभेत्रेयामान्यद्रमा लेक्ष्रद्रद्रिकेत्रेयोग्य		
Gln422-Tyr435	(241)	क्षीत्रव्यक्षिण में बाद्याना है सम्बोद्धीर राष्ट्रिक		
Arg426-Lys432	(241)	estrait nackedamates/falts/		
Arg426-Gly431B	(241)	स्तिक्षामस्त्र द्विशक्तकादिकार्यः । इतिहासस्य द्विशक्तकादिकार्यः ।		
Asn425-Lys432 Consensus	(241) (241)	GAGATCGTGCTGGAGAA		
00.1301.343		281	COTOACCGAGAAC	320
Ile424-Ala433	(281)	Medicy of the real date with the second		
Trp427-Glý431	(281)	व्यक्तिक व्यक्तिक विकास विकास विकास करिया है।		
Gln422-Tyr435B	(281)	constructions proceeding the first and		
Arg426-Gly431	(281)	द्रश्यात्त्रकृत्यः। इत्रेत्रीयकृत्यः		
Ile423-Met434	(281)	actions/politalsocopysesses/comminity		
Gln422-Tyr435	(281)	लक्ष्यक्षराव्यक्ष्मित्रकार्यक्षराव्यक्षरा		
Arg426-Lys432	(281)	cjoji ktježi pipovi prije, lje Kčijak šeje		
Arg426-Gly431B	(281)	etering elitary sulfrish in including		
Asn425-Lys432	(281)	हाक्रम्भेरवर्ग्निर्गिर्वेश्वर्ष्टिश्रमेहक्षित्रहा	the plansidentic	<u>च्येत्रक्रमञ्जूष</u> स्टब्स्
Consensus	(281)	GGAAGAACAACATGGTGG	SAGCAGATGCACG	AGGACATCAT 360
Ile424-Ala433	(321)	mater all a lactocastic contributions	College Taller Section	
Trp427-Gly431	(321)	entrale configuration and administration		
Gln422-Tyr435B	(321)	रूपम्हण्डल्स्स्ट्रास्ट्रास्ट्रास्ट्रास्ट्रास्ट्रास्ट्रास्ट्रास्ट्रास्ट्रा		
Arg426-Gly431	(321)	Condition the control of the control		
Ile423-Met434	(321)	(2017年) 2月10日 (2017年) (2017年)		
Gln422-Tyr435	(321)	राम्हाराम्बर अस्तराम् अस्तराम्		
Arg426-Lys432	(321)	र प्राचार के स्ववसंत्र (क्षिप्रेय) र जाता है।		
Arg426-Gly431B	(321)	erret appeared by the property of the property		
Asn425-Lys432	(321)	Markett in the administration that the		
Consensus	(321)	CAGCCTGTGGGACCAGAG 361		
Ile424-Ala433	(361)	ः स्टरण्यस्य । विकासमान्त्रे में स्टान्ट्रियम् (स्ट्रेट्रिक्ट्रि	to the production of the second	
Trp427-Gly431	(361)	wate interespendent medien, ethalic		
Gln422-Tyr435B	(361)	The later that the first to be the think of the contract of th	- Andrew Charles - Andrew Control of the Control of	
Arg426-Gly431	(361)	As it in the control of the control of the		
Ile423-Met434	(361)	देश व राहाद्वीत्नगढर । स्त्वाली मेद्रोग्रहार		
Gln422-Tyr435	(361)	MEXICULAR SOCIAL PROPERTY.		
Arg426-Lys432	(361)	गता गिर्दा होट नेत्र महाल द्याग्या गुरू		
Arg426-Gly431B	(361)	प्राक्ताव्यक्ताहरू, स्वाह्म स्वतंत्र ।		
Asn425-Lys432	(361)	रखिए। एस् स्ट लिक संदर्भ स्टेस्ट्रिकेट		
Consensus	(361)	ACCCCCTGTGCGTGACC		
		401		440
Ile424-Ala433	(401)	भ•द्याराज्यात् (अत्यक्षात् क्षात् । ब्रह्मात् । ब्रह्मात् ।		
Trp427-Gly431	(401)	मेर्चा १९१० के हिंदी हो स्वरूप हो मेर्च १९११ मेर्च		
Gln422-Tyr435B	(401)	theteir contingentationite lostifitiesis	utwiftelmszad infilesty	ૹૡ૽ઌૹૻૡૡ <u>ઌ૽</u>

FIG. 4B

FIG. 4C

WO 00/39303		18 / 65	PCT/US99/31272
Gln422-Tyr435	(601)	सक्रदशांद्रांकवृद्धां भूषां कृषां विद्यां कृषां कृषा (वृद्धां कृष्टा विद्यां	Muchalete Chine terms of
Arg426-Lys432	(601)	etala infinitala (a fa	
Arg426-Gly431B	(601)	व्यक्तित्रीयं,व्यविद्विद्वित्रीत्रीत्रीयद्विद्वित्तिवित्रीत्वित्रीत्वातः स्तूत्राद्वात्तर्भववि । (६.)	
Asn425-Lys432	(601)	estidos acteradas prodos prodos prodos constituiras estados en entre estados estados entre entre estados entre entre estados entre ent	
Consensus	(601)	GCCTGCCCCAAGGTGAGCTTCGAGCCCA	
	(/	641	680
Ile424-Ala433	(641)	प्रदेशक्त्रसंक्ष्यंक्ष्यं हिन्द्रस्थात्। स्थान्यक्ष्यं स्थान्यक्ष्यं स्थान्यक्ष्यं स्थान्यक्ष्यं स्थान्यक्ष्यं	and the second s
Trp427-Gly431	(641)	प्रथमिस्ट सर्विकृतिहास्य प्रदेशिक । मेलसर्विकृतिक	
Gln422-Tyr435B	(641)	अधीरित कि अंशवित हो होता है। वार्त के अधीरित हो स्वापित के अधीरित कि अधिर होता	
Arg426-Gly431	(641)	अवभवता विविध्य वात्राम् कृष्टी संबद्ध । अवस्ति व अवस्ति।	
Ile423-Met434	(641)	were the following the state of the section of the	
Gln422-Tyr435	(641)		
Arg426-Lys432	(641)		
Arg426-Gly431B	(641)		
Asn425-Lys432	(641)	भागम् स्थाने विकास स्थापन स	
Consensus	(641)	ACTGCGCCCCGCCGGCTTCGCCATCCT	
Consensus	(041)	681	720
Ile424-Ala433	(681)	ાં કે તે માં મેં મેં આવે ફેર્માને જીવે કે કે માટે જે કે કે માટે માટે કે લક્ષ્યો છે. જે માટે કે માટે કે માટે કે 	
Trp427-Gly431	(681)	करमानुस्य मार्थित स्थानिक विकास में मुक्ति हो हो हो हो हो है	
Gln422-Tyr435B	(681)	क्षरे के देखा है । इस का	
Arg426-Gly431	(681)	द्वाराच्याकृतकारकश्चात्रकारभ्याकृतिकारकृतकार्यस्ति । १००५ कर	
Ile423-Met434	(681)	auniquismo printatival l'utologicació (com en les irolo	
Gln422-Tyr435	(681)	क्षेत्रकारकारकेरे देव सार्गाचनकार हत्याचा एकत्। जाता को लाहनाव स्टिन	Staffichers in the country
Arg426-Lys432	(681)	क्षेत्रकृष्टकारकारकोकाका वर्षेत्रकृष्टकारकारक र विदेशीतालीक्ष्रिकार	
Arg426-Gly431B	(681)	strategistrent (\$60%) attach the best sile in tentions	
Asn425-Lys432	(681)	हरकार प्रकार का वाल में के बहुत हैं हैं हैं है	
Consensus	(681)	CAAGAAGTTCAACGGCAGCGGCCCCTGC	ACCAACGTGAGC
T1-404 D1-400	/2011	721	760
Ile424-Ala433	(721)	में खेर हरता है (ब्यू में बर्ड संपाली हैं है। कि में हो हो ब्यू हैं में में है है।	
Trp427-Gly431 Gln422-Tyr435B	(721)	And the Coloration of the Colo	Selection of the select
Arg426-Gly431	(721)	Asset to the second of the second sec	
Ile423-Met434	(721) (721)	une case divelgées adactions écles (a conseil)	
Gln422-Tyr435	(721)	afters of Michel Architectic and promate restaurant of the American for the American Community of the American Community o	
Arg426-Lys432	(721)	nations is an interestinately laterated in the residual following and the r	
•			
Arg426-Gly431B Asn425-Lys432	(721)	्रेक्षा विभावित्वे । प्राप्तिक स्वत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्ष	
Consensus	(721) (721)	ACCGTGCAGTGCACCCACGGCATCCGCC	
Consensus	(721)	761	800
Ile424-Ala433	(761)	clos satelenigelesspelichnenisklerleiste varrechtingelate 191	
Trp427-Gly431	(761)	the material of the property of the second o	
Gln422-Tyr435B	(761)	enviolensia secta of class envisore tropulation inclets	
Arg426-Gly431	(761)	त्रका । प्रकृतिक विकास विकास विकास करते । केरता की क्षेत्रक किला की की कार्या की	
Ile423-Met434	(761)	place of a classical statistical by the construction of the finite force.	
Gln422-Tyr435	(761)	राह १० (प्रदेशक रहेदेश सम्बन्धक प्राथम अस्ति । अस्ति ।	
Arg426-Lys432	(761)	ระบาร กายรัส เมื่อรู้จากสัดเอก็ระบบรัชการสารกับการสารการสารกระบบรัช	
Arg426-Gly431B	(761)	्य र प्रस्ति । संकार स्वर्ग महोत्रास्त्री स्वरूप नेवते । प्रास्त्री ।	
Asn425-Lys432	(761)	were their instructed the homestales are restricted able to	
Consensus	(761)	CCCAGCTGCTGCAACGCCAGCCTGGC	
		801	840
Ile424-Ala433	(801)	सम्पन्न का सम्मन्त्र के अन्तर के अन्तर का	क्षा चित्र शिक्ष क्षेत्र अस्ति ।
Trp427-Gly431	(801)	लक्ष्यः बोत्रुत्ताव्यवाचिवांत्रिवाद्यंत्राप्तंत्रम् व्यक्षात्राक्षात्राच्या	interestination
Gln422-Tyr435B	(801)	लक्ष्यत्याम् इति होत्ये होत्ये होत्ये होत्ये होत्या होत्या होत्या होत्या होत्या होत्या होत्या होत्या होत्या हो	<i>श्चाहोहोहोहा</i> अन्य श्राहरी है
Arg426-Gly431	(801)	यक्षभक्षाम् अंवेदालेप्रदेशकोप्रकृष्णप्रदेशकोप्रदेशक	म् १ व्यास्त्र स्ट्राप्ट स
Ile423-Met434	(801)	द्यवभारम्भूभावद्वद्वांद्वभावद्वाक्षम्यभूद्वाभूद्वाः स्थाद्याः (हृद्वस्तान्त्रीक	
Gln422-Tyr435	(801)	लेक्सल एक एवं एक	
Arg426-Lys432	(801)	संब्हर स्टब्स्य स	
		The state of the s	

FIG. 4D

Arg426-Gly431B	(801)	र रहेभ्ये क्रियं होते हो है। हो हो हो हो हो हो है है।
Asn425-Lys432	(801)	લાનાનુ ભાગમાં લોકો બાલો કાર્યો કાર્યો હોય કાર્યોના કાર્યો છે. તે કાર્યોના કાર્યો કાર્યો કાર્યો કાર્યો કાર્યો ક
Consensus	(801)	GGTGATCCGCAGCGAGACTTCACCGACAACGCCAAGACC
		841 880
Ile424-Ala433	(841)	randurban jähitete irtalminjaktekitaiatrinistialitenin aleitelekkapterisineriekt
Trp427-Gly431	(841)	रामस्वर रामस्वर में के उने कर राज्य में कार कर राज्य कर राज्य है। यह सामस्य के सामस्य के स्वर्ध कर राज्य है।
Gln422-Tyr435B	(841)	
Arg426-Gly431	(841)	
Ile423-Met434	(841)	
Gln422-Tyr435	(841)	कार्यक्षात्रकारो रामा स्वरंगित्रकार क्षाकार स्वायं स्वरंगित स्वरंभ राम करता सामा स्वरंगित स्वरंगित स्वरंगित स्
Arg426-Lys432	(841)	ાં સાફેલ ક્લામલ લ્ફ્રેસલ અલેલન્ડ માન્સ સ્વાર્ક લિકા મેલ્સ મિલા કેલ્સ કેલ્સ કેલ્સ માન્ય માન્ય લેલા કેલ્સ કેલા મ
Arg426-Gly431B	(841)	cente, interest to altitudate, intimatacious estimates calificiates per established syst
Asn425-Lys432	(841)	व्यान् र राम प्रवृत्तिमा द्वित्ते हो हाम (कारकार होकार हो को में कि कार्म संस्थान होता होते । मृत्ये में हो स्
Consensus	(841)	ATCATCGTGCAGCTGAAGGAGCGTGGAGATCAACTGCA
		881 920
Ile424-Ala433	(881)	ान्द्रशब्दिको । एकान् केरणपुर्वकार १५४० विकास
Trp427-Gly431	(881)	न्त्रेत्रास्त्राचीत्राक्ष्राक्ष्राक्ष्राक्ष्यक्ष्यक्ष्यक्ष्यक्ष्यक्ष्यक्ष्यक्ष्
Gln422-Tyr435B	(881)	eforete, etalololorus ensumerrom etalo lettosisotototoko keristololorus eta
Arg426-Gly431	(881)	व्यक्तिम् द्वारा (द्वाराम् प्रदेशम् वर्षायम् । वर्षाय द्वारा हेत्या वर्षाय वर्षाय वर्षाय वर्षाय वर्षाय वर्षाय वर्षाय
Ile423-Met434	(881)	ी, जेर 'चावक दिर्गर 'बेप्याचार हर जो अपने देशके. वेट 'ब्रांबिकार सुंबर हुंचा रहेगा के सुन्नी के लेखें दुर्जा बहु
Gln422-Tyr435	(881)	જાયો પર્વાર ભાગમાં આવિતામાં ભાગમાં આવે છે. આ વાર્ષ જાણા આ પાણી વિજય કરવા છે. કરો આવે છે છે
Arg426-Lys432	(881)	क्षत्र कि । वह । १९, १९, १८ वर्ष में १९ १९ १९ १९ १९ १९ १९ १९ १९ १९ १९ १९ १९
Arg426-Gly431B	(881)	cjujetakon i josepine napolinakennokeje eliminatakijen ind. Alekonikije eke
Asn425-Lys432	(881)	अंदर्शकेर्यक्षेत्रभावत्रप्रसारमञ्जूते । १८ १८ १८ १८ १८ १८ १८ १८ १८ १८ १८ १८ १८
Consensus	(881)	CCCGCCCAACAACACCCCGCAAGAGCATCACCATCGG
		921 960
Ile424-Ala433	(921)	द्राकरातान्त्रात् तत्त्ववित्राद्यक्षप्रकाकात्वातां का अवश्वासामा सम्बद्धाः का कार्यक्षात्रा कार्यक्षात्रा । स
Trp427-Gly431	(921)	इत्यान्याया । । वर्षेत्राम्य कार्यक्षात्रा । वर्षेत्रा वर्षेत्रा ।
Gln422-Tyr435B	(921)	मार्थका में बहुता हा त्याव देशका अन्यक्षण अनुसर्वक क्षेत्र का मार्थक में क्षेत्र के अनुसर्वित स्था
Arg426-Gly431	(921)	कर दिस्मिन्द्रपुर्वाक्ष्मिन्द्रम् नाम्याद्रमान्द्रमान्द्रमान्द्रमान्द्रमान्त्रमान्द्रमान्त्रमान्द्रमान्द्रमान्
Ile423-Met434	(921)	Signature of a gradient the hopeful content to the tracket which
Gln422-Tyr435	(921)	commercial contractions and the contraction of conservation of the following strategy and strategy and strategy and the contraction of the contrac
Arg426-Lys432	(921,)	The Multiple District of the manners rate from a retending to a property of the section of the s
Arg426-Gly431B	(921)	१९७८ में मृत्यादर के दिल्ला है। १८५ के १९५१ के प्रति १९६५ को एक प्रति होता है। इस दिल्ला के अपने प्रति हो प्रकार
Asn425-Lys432	(921)	्रकार्याः प्रश्तिकान्त्रीय (प्रांतर प्रत्यमानात्त्राचार्यः प्रद्रवारः) । स्वत्राप्तिन्ति हेल्लान्त्राप्तिन प्रदेशहः (प्रतिक्री
Consensus	(921)	CCCCGGCCGCCTTCTACGCCACCGGCGACATCATCGGC
		961 1000
Ile424-Ala433	(961)	्रात्त । इत्यात् विकार
Trp427-Gly431	(961)	nation to accipitate joi training is an ouncipolitic changing included in include in confi
Gln422-Tyr435B	(961)	eaugestann einege anwer von jest mant diete inn die Gestellerteile bereich
Arg426-Gly431	(961)	than there exists format in order in elements, there have played an expensive the
Ile423-Met434	(961)	Ale manistionistratura proportionistrationed menantrebalisted highway
Gln422-Tyr435	(961)	Base to block of a through to be the origination for some the telefold of the base of
Arg426-Lys432	(961)	especial six to the tradeury process and energy consister to the production of the tradeury process.
Arg426-Gly431B	(961)	रमानुकर्माता, जोरहातुर पुर्दाती एक क्रिकेट्रीयट्री प्रदेशनेचा बर्ड्ड राज्यदेशीद्रुट्राचीचार्यक्रिकेट्सक्रिकेट्
Asn425-Lys432	(961)	בוניקונים אין איני ופוניון וווניון ווייניון וווניון ביין מוניון מוניון איני וויינין איני וויינין וווניון ביין
Consensus	(961)	GACATCCGCCAGGCCCACTGCAACATCAGCGGCGAGAAGT
		1001 1040
Ile424-Ala433	(1001)	द्रांच्यक्षेत्रके क्षेत्रकृतिकाले अस्तरक्षक्षेत्रकार क्षेत्रक्षेत्रकार क्षेत्रकृतिकार क्षेत्रकार क्षेत्रकार का
Trp427-Gly431	(1001)	लेक्षां हर्षा हरू दूर हर्षा हर्षा का विकास स्थान हरू हरू हर्षा है। इस हर्षा हरू हर्षा हर्षा हरू हर्षा हर्षा हरू
Gln422-Tyr435B	(1001)	cicitis in the control of the contro
Arg426-Gly431	(1001)	etatopale trait estilat formetraticieste japraciojan taricie ir kilatatici de fletera
Ile423-Met434	(1001)	egestynte freige vile ig in nesthafegenjichtel pychae finferie i beiteil nitethytaen en
Gln422-Tyr435	(1001)	निकारमातः इतिहास्ति १,४०४वनिमार्गादाऽअस्तिमान्तिवातः । एरावनिमार्गादाङ्के देश्वामातिक्
Arg426-Lys432	(1001)	eterraserraterre ete nechrade henkreienanvele fandeloinerritelete
Arg426-Gly431B	(1001)	વ્યુવસાયના માર્કા કર્યો કર્યા છે. તેમ જ માર્કા કર્યો માર્કા છે. તેમ જ માર્કા કર્યો કર્યો છે. તેમ જ માર્કા કર્યો છે જે
Asn425-Lys432	(1001)	elegistates ratus in the solitor in the solitor of
_	-	

FIG. 4E

_		
Consensus	(1001)	GGAACAACACCCTGAAGCAGATCGTGACCAAGCTGCAGGC
		1041 1080
Ile424-Ala433	(1041)	श्राक्ताम् साम्याद्वाराष्ट्राच्याकृतिकृतिकृतिकृतिकृतिकृतिकृतिकृतिकृतिकृति
Trp427-Gly431	(1041)	edest/edustrespeter supplicat/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/enticles/
Gln422-Tyr435B	(1041)	पुर प्रिक्त भवाद राष्ट्रभावे वेद पर्देशकार्यस्त्रहरूका प्रदान एक एक मार्क्स स्वताहरूक राष्ट्रका स्वताहरूक । पर
Arg426-Gly431	(1041)	લોક્ટ્રોફર્સિયામ હતા તે દોલા ભાગે છે. કુંકા પ્રથમિક હિતા પાળી લોકા ખુલી તે છે. કરો પ્રદેશ કરો જે ભાગ હો કરો છે.
Ile423-Met434	(1041)	。 一個社會無疑問題的影響的特別的影響的影響的影響的。 中國的影響的影響
Gln422-Tyr435	(1041)	स्ति । त्रिका त्रामान । व्योग देवा त्रिका व्यवस्था स्थान स्थान स्थान स्थान स्थान स्थान स्थान । व्यवस्था स्थान स्थान स्थान स्थान ।
Arg426-Lys432	(1041)	राहरू क्रोडा र मा अस्तर एक होन्यर एक होल्या स्टाइस्टाइस स्टाइस क्राइड है । हे स्था प्रश्नामा अस्तर हो दहिए होन
Arg426-Gly431B	(1041)	म्बर्कातात्रक्षकृतिकार्यात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात्रक्षात
Asn425-Lys432	(1041)	्या १५८ मा । बाद विकास क्षेत्रका स्थाद १५८६ । इस्ता क्षेत्रका स्थाप विकास ।
Consensus	(1041)	CCAGTTCGGCAACAAGACCATCGTGTTCAAGCAGAGCAG
		1081 1120
Ile424-Ala433	(1081)	राजी एकार्य (देव के इन्हेंन क्षितक्ष्म) हैन्द्रिक सन्त्रे देवा कार्य है। स्विक रीत क्षितिकों हैन रेह्
Trp427-Gly431	(1081)	contraternamentalistics and expensive and present the expensive present the pr
Gln422-Tyr435B	(1081)	etalaretikeratus kaletaktektaagoisingustus erenteliteojogis, jatattati har e
Arg426-Gly431	(1081)	cloie integrieur i prisétatudiféry aranticita autouve projecte in qui récultair fa
Ile423-Met434	(1081)	enegotefetetesty, setafotetiffetiffetiffetiffetiffetiffetiffet
Gln422-Tyr435	(1081)	कार एक प्रकार कर में कर हो हो हो हो है है के के किया है
Arg426-Lys432	(1081)	elementariam eleja monifelik elejenika ken en mannente park en ken e
Arg426-Gly431B	(1081)	1964 - Kerning and golden being bereich gereichte werten der begeben werden bister gebiede bie Fil
Asn425-Lys432	(1081)	igals igain every are master tene physiological properties and control quarte
Consensus	(1081)	GGCGGCGACCCCGAGATCGTGATGCACAGCTTCAACTGCG
		1121 1160
Ile424-Ala433	(1121)	स्परवर्त्तायकः अन्तर्भाषार ।।। जन्मानकोत्त्रपृत्वेकराक्षमध्या प्रदेश विद्वार्द्धार ।। ।।
Trp427-Gly431	(1121)	त्रात्रेद्रदर्शनाम् मृत्याः भेटामा भेजासम्बद्धाः भन्ते व्यक्तिस्तर्भक्ताः । व्यक्तिम् वर्षाः भन्ने ।
Gln422-Tyr435B	(1121)	Arginia faktuat ilgi salla faktelahilik pidekapetualfit esikitotti mediditeri ilg
Arg426-Gly431	(1121)	ક્ષરનું કોક્સ્ટર (કોક્સ્ટર) (કાર્યું એ, સોર્ડ-એ, કેટ પ્રકાર સ્થાપોલે સ્થાપેલ ક્ષર કરો કરવા કો કોર્યું કોર્યું છ
Ile423-Met434	(1121)	characters and execut programs in paracipal scribble; and a function by the six of the projection of
Gln422-Tyr435	(1121)	दोन दोहोर क्रियमिक १४ (महोट) दोमेर देशर प्रेस्ट स्थाप क्रियम स्थाप । स्थाप क्रियम स्थाप स्थाप स्थाप स्थाप स्था
Arg426-Lys432	(1121)	ers tesen sotas in neintate ingge interestatables until standarde situation (
Arg426-Gly431B	(1121)	the the ending and any appropriate the properties of the state of the
Asn425-Lys432	(1121)	Megana e jester, et e ja omi distribit strokstome, ena e etasje distribit st
Consensus	(1121)	GCGGCGAGTTCTTCTACTGCAACAGCACCCAGCTGTTCAA
		1161 1200
Ile424-Ala433	(1161)	१९७१म म्याहरू २६ आस्पूरियहे क्योर स्टेस्ट्रिक्स १९८५ हो स्टेस्ट्रिक्स स्टेस्ट्रिक स्टेस
Trp427-Gly431	(1161)	ार १८८८ । विदेश संदेश क्षेत्र का संस्थित । क्षेत्र का स्थान क्षेत्र का स्थान का स्थान का स्थान का स्थान का स्थ
Gln422-Tyr435B	(1161)	ateminary of securioristic policy from a profit of the profit of the following of the final policy of the
Arg426-Gly431	(1161)	ing of the contribution of
Ile423-Met434	(1161)	्य विकास स्थानिक विकास विकास विकास विकास विकास के विकास क
Gln422-Tyr435	(1161)	જ્યાર, જાઈકાર, પર (અમુનાર) પ્રજનિ પ્રજી પ્રદેશિકોની ઉંચર અલ્લાન્ટ વર્કોસ્ટોણી પ્રજી અમેરી કરો છે.
Arg426-Lys432		with the material contractive manufactures and additions
Arg426-Gly431B	(1161)	reactions of the county has plantable and present and the second of the county of the county and
Asn425-Lys432	(1161)	and a successful to the demonstration of the state of the
Consensus		CAGCACCTGGAACAACACCATCGGCCCCAACAACACCAAC
T) 101		1201 1240
Ile424-Ala433		त्यस्य । १९८ मा मा युक्त हरित है कि इंग्रह्म द्वारा हरित है हिम स्वार्थ के स्वता है महिन है स्वार्थ —
Trp427-Gly431		द्रोद्या हेत्र महत्त्व । विदेशहोद्दानीय ब्यादिन के व्यवदानी वृद्धा कर १५७० प्रतान व्यवस्था पृत्री के प्रवृद्धी
Gln422-Tyr435B		क्षेत्राः कृतान्त्रेरमा वृत्तिर्वेनो कार्यव्यक्तर्यक्षिति व्यक्षित्र कृतिनाव्यक्षिक्रयोष्ट्र
Arg426-Gly431		annic processors and the sequence of the seque
Ile423-Met434		them in the property of the pr
Gln422-Tyr435		eunte bage jehne einde der jegen fangelieten auf die beste fan it Statische dige
Arg426-Lys432		atick, jazo jestereje igi up-a jihlego rozoviklejn goslati štolika izritgeli. Štalašna iz svijuojij
Arg426-Gly431B		લામાં કર્યા હો કારમાં હો કેટ કુંદ કરાયા હો છે. ભૂચ્ચા ફાર્ણક કરાયેલ કર્યા હા માર્ગ છો કહેર કરાયા કામ કુંદ કુંદ
Asn425-Lys432		stoje mas jegla ije strojak salasij daju, ju jeja ir toje saruja izanje je sidensejni objer jela, jela,
Consensus		GGCACCATCACCCTGCCCTGCCGCATCAAGCAGATCATCA
		1241 1280

FIG. 4F

21 / 65

Ile424-Ala433	(1240)	दिविल्पिरिक् ह - विकासिर विकासि
Trp427-Gly431	(1241)	सम्CGCTGG द्वाष्ट्रवाधानुस्थात्वावन्त्रभादावन्त्रभावतान्त्रभावतान्त्रभावतान्त्रभावतान्त्रभावतान्त्रभावतान्त्रभ
Gln422-Tyr435B	(1234)	
Arg426-Gly431	(1241)	अवेCCCCC वेबासम्बद्धकारम्बद्धकारम्बद्धाः ।
Ile423-Met434	(1237)	
Gln422-Tyr435	(1234)	
Arg426-Lys432	(1241)	AMCGCGGC सन्देविते कार्यान्त्रन्त्राध्ययस्य स्थापना विद्यान्त्राध्ययस्य स्थापना विद्यान्त्रा
Arg426-Gly431B	(1241)	ACCGCGGCA CCCCCCNVCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
Asn425-Lys432	(1241)	the GCBCC of the excitorist of the form of the state of the
Consensus	(1241)	AC GGCGGCAAGGCCATGTACGCCCCCCCCATCCG
	, ,	1281 1320
Ile424-Ala433	(1269)	1020
Trp427-Gly431		e per executante in the fight in the production of the first of the state of the first of the second
	(1281)	्रदेशका सम्प्रमाधिका । द्वारोश कार्याल कार्या । प्राथमिका १८ मा । व्यापन व्यापन व्यापन । व्यापन व्यापन । व्याप
Gln422-Tyr435B	(1257)	त्रहित्साल क्षेत्रिया स्थितं स्टिल् हित्या कर्या क्षेत्रे क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र स्थ
Arg426-Gly431	(1281)	भारताच्या र १०५५म् देवा सहितानोही दक्ष ने स्थित है। यह स्थापित दार स्थापित स्थापित स्थापित है। स्थापित स्थापित
Ile423-Met434	(1263)	का प्रकार का क्षिप्रकार के होते हैं है
Gln422-Tyr435	(1257)	अवाद्यक्ष द्रोमेद्रमेश्रेश्वेद्रस्तितः संदेशितेद्राक्षेत्रम् । वस्यत्यामाश्रद्धेन्त्रमेश्रद्धियाः वस्य
Arg426-Lys432	(1281)	સ્ત્રિયાના કરો કરો હોયા છે. <mark>છે. છે. છે. છે. છે.</mark> જે માને કરો કરો છે. જે માને કરો છે. જે છે. જે છે. જે છે. જે છે.
Arg426-Gly431B	(1281)	स्वास्त अस्ति। संसाद्देशेषुर्वे स्वर्धानस्ति। स्वरंगानस्ति। स्वरंगानस्ति। स्वरंगानस्ति। स्वरंगानस्ति। स्वरंगानस्
Asn425-Lys432	(1275)	- into fighter and expectation after the configuration become and
Consensus		
Consensus	(1281)	CGGCCAGATCCGCTGCAGCAGCAACATCACCGGCCTGCTG
T1 = 404 - D2 - 400		1321 1360
Ile424-Ala433	(1309)	र के नका के कुरिया (द्रारक्त क्षेत्र के कि
Trp427-Gly431	(1321)	क्षेत्रमा हरा हार हार होते होते होते होते होते होते होते होते
Gln422-Tyr435B	(1297)	esta, wasta ke jumera ta kapis estata kishashisha kinda kinda kinda kinda da sana asia wasiake wati
Arg426-Gly431	(1321)	कार हो एक वित्र देवा देवा होते हो हो हो हो हो है जिस हो है
Ile423-Met434	(1303)	क्षांतर प्रदेशक द्वित स्वापनी स्वापनी स्वापनी स्वापनी प्रतिकार प्रतिकार प्रतिकार स्वापनी स
Gln422-Tyr435	(1297)	ning provided graditation of the control of the provided control of the
Arg426-Lys432	(1321)	રમામાત્રાના સંવતિ દ્વારા કરે કે દ્વારા કર્યું છે. તે કે
Arg426-Gly431B	(1321)	anyentelengereistigestricterantikalenterranastraturatura (merite
Asn425-Lys432	(1315)	Carries of the same felt that the gradient for the process of the first field of the same of the first field of the same of th
Consensus		
Consensus	(1321)	CTGACCCGCGACGCGCAAGGAGATCAGCAACACCACCG
73 404 53 455		1361 1400
Ile424-Ala433	(1349)	त्वारोक्षर व पुरस्कानम्बद्धि व्यक्षाद्धान् । यानीक्षानीयो, त्वाराच उपमुन्तव साक्ष्यों व विविद्यों । विवि
Trp427-Gly431	(1361)	that the states telestalated the regularity frame state state in the second telestal the
Gln422-Tyr435B	(1337)	agence dis addictation (conjunction) on a systematical production in logarity population
Arg426-Gly431	(1361)	never existing appreciate constitution of the property of the section of the sect
Ile423-Met434	(1343)	त्यस्य विकास विकास हो । विकास
Gln422-Tyr435	(1337)	स्य के एक असीर विद्याल हो हो हो हो है। इस स्वार के स्वार के स्वार के स्वार के स्वार के स्वार हो है। इस स्वार क
Arg426-Lys432	(1361)	पुरुषक १५ जन्मात । इस्ति हिस्सित हिस्सित है स्टिनिस्ट । इस्ति है सम्मित है से स्थान है है
Arg426-Gly431B	(1361)	त्रात्र कर्मक निर्माणक कर्मक विश्वविद्यालया क्षेत्र क्षेत्र क्षेत्र कर्मक विश्वविद्यालया कर्मक विश्वविद्यालया
Asn425-Lys432		
-		indexistantification of the process
Consensus	(1361)	AGATCTTCCGCCCCGGCGGCGGCGACATGCGCGACAACTG
71.404 51 :55		1401 1440
Ile424-Ala433		als from interestablishing presentations and topological additional features of the section of t
Trp427-Gly431	(1401)	and the spiritage of the state of the spiritage of the state of the spiritage of the spirit
Gln422-Tyr435B	(1377)	न्यत्राक्षात्रः स्वत्रात्रेत्रे देविके स्वतिक्षेत्र विक्रका द्वित्र विक्रका स्वतिक विक्रका स्वतिक विक्रा कार अस
Arg426-Gly431		का प्रदेशको प्रमाणकारकार काविमास हो प्रभाव दे कि एकाव है। तेर है र प्रभाव का कावी के क्षेत्रकार समावेश हो के प
Ile423-Met434		cluses, than of challenges in Mental shaped sayou had challenge that label in a who
Gln422-Tyr435		ार्यः सः इत्यः विभवति प्रितास्ति हिन्द्राच्याः स्वीतं प्रस्तवस्य स्वास्त्रास्त्रास्य स्वीतः स्वीतः स्वीतः स्वी
Arg426-Lys432		
		apace, stretelestrate infentita statiefithiles, a feleage restriction factories
Arg426-Gly431B		ste je te erkets je krelen ke, sie te detre skrive krete fra gerekke it ke transete i te
Asn425-Lys432		द्भिक्ष कर याम्य सम्मुद्धि हो मूंद्रो संग्रह के एक एक एक एक मुक्त स्था मुक्त स्था है। स्था स्था स्था स्था स्था
Consensus		GCGCAGCGAGCTGTACAAGTACAAGGTGGTGAAGATCGAG
		1441 1480
Ile424-Ala433	(1429)	one with the celebrate the festers of the confinction of the festers of the source of the confined of the conf
Trp427-Gly431		i in behi yinege kantay ya fajir baliyin baliyin kali yayin bibi, into yini indepina bi tek ini fa
-		

FIG. 4G

Gln422-Tyr435B	(1417)	the arthursteleta describiretation to the artificial and
Arg426-Gly431	(1441)	
Ile423-Met434		
	(1423)	
Gln422-Tyr435	(1417)	
Arg426-Lys432	(1441)	our in la lagrandese seant convoluter clauses, est est ceasus debitos papillancias canon de
Arg426-Gly431B	(1441)	
Asn425-Lys432	(1435)	
Consensus	(1441)	CCCCTGGGCGTGGCCCCACCAAGGCCAAGCGCCGCGTGG
		1481 1520
Ile424-Ala433	(1469)	ंत्रहोत्रकोत्रवास्त्रहार 'कार्यकोर्डे विद्राही होता हो दर्श क्रिया हो है। क्रिया
Trp427-Gly431	(1481)	intere to allegate tense proprietatata tala la tense proprieta parada cala la comensiste de la comensión de la
Gln422-Tyr435B	(1457)	national principle stream state, or elected a non-angle solvest analytical principles of a
Arg426-Gly431	(1481)	भारत्यका जन्मक्षिकारोग गर्यहार्वकात्रमाना शस्य क्षाप्तस्य हिस्सार्वकार्यकार्यः ।
Ile423-Met434	(1463)	त्रात्रात्रकात्रियाः कामानाक्ष्येभागतान्त्रीवृत्रियाः व्यक्ते प्रात्तावृत्तेवाद्याः विद्युप्तर्थः । व
Gln422-Tyr435	(1457)	તા પાક ત્રાફાઈ જિલ્લાન કાર્યમાં ભૂતિમાં ભૂતિ કાર્યા કરતા છે. કાર્યા પાક લોકોને જો જેવી છે છે છે છે છે છે છે છે
Arg426-Lys432	(1481)	कर्राव्यक्रिका । वर्षका कर्षका वर्षका वर वर्षका वर
Arg426-Gly431B	(1481)	रवान्त्रद्वातायाचा व्यवस्थात् । स्वतः अस्ति । स्वतः । स्वतः । स्वतः । स्वतः ।
Asn425-Lys432	(1475)	त्तावर्त्वेशस्य ब्हेळाल्त्वेश्वेषम् १५ (इक्षेट्रा ब्हेब्रिक्तः) स्वयोध्यात्त्वेष्ट्रे विष्यवर्त्वात्त्रे व्यवस्थिते ।
Consensus	(1481)	TGCAGCGCGAGAAGCGCGCCGTGACCCTGGGCGCCATGTT
		1521 1560
Ile424-Ala433	(1509)	्याच व्यवस्थात व्यवस्थात वर्षेत्राच्याच्याचेत्राच्याच्याच्याच्याच्याच्याच्याच्याच्याच्य
Trp427-Gly431	(1521)	२२ मा प्राप्तिक । प्राप्तिक विद्वार के विद्वार के प्राप्तिक के स्थापन के अपने कि के प्राप्तिक क
Gln422-Tyr435B	(1497)	अंकर के मान्या के अन्य के अंकर के अंकर के अंकर के अंकर में मान्य के अने कि स्थान के स्थान के स्थान के स्थान के
Arg426-Gly431	(1521)	Albert artists in the artists of the officers and the second of the seco
Ile423-Met434	(1503)	ं में पाप । दर्शाने पर एक आरोबार देशन्त्रीयांका पेसरे हैं शर्पायुरंत एक में प्रस्तरूप्तरीय देश कुल्ला हुन हैं
Gln422-Tyr435	(1497)	्रवाहरूपानिकार व्यवस्थान स्वाहर्षा स्वाहर्षा विद्या हो स्वाहरूप स्वाहरूप स्वाहरूप स्वाहरूप स्वाहरूप स्वाहरूप स
Arg426-Lys432	(1521)	वीक्रमकृतिकृतिक १९४५ । ए तुर्वे द्वारामानुस्ति । क्षेत्रक शुक्तावद्दि । १९५५ १९५५ से स्मित्राम् स्ट्रान्ट्रस्य स्थाप
Arg426-Gly431B	(1521)	कालामान्द्रवाद्यक्रमान्द्रवामान्द्रवामान्द्रवाद्यविद्यात् विद्युवाद्यवान्त्रकृत्यान्त्रम् द्रिक्षेत्रकृत्यान्द्
Asn425-Lys432	(1515)	ાલકારા (ફોલાલુક મોર્યુલ) દેખું દેવાલા તે એક્ષુલોકો પ્રાપ્ય છાલા કરિયત કરવા કર્યો કરો છે કે કો મોકા હોલા છે છે
-		
Consensus	(1521)	
Consensus	(1521)	CCTGGGCTTCCTGGGCGCCGCCGGCAGCACCATGGGCGCC
		CCTGGGCTTCCTGGGCGCCGCCGGCAGCACCATGGGCGCC 1561 1600
Ile424-Ala433	(1549)	CCTGGGCTTCCTGGGCGCCGCCGCAGCACCATGGGCGCC 1561 1600
Ile424-Ala433 Trp427-Gly431	(1549) (1561)	CCTGGGCTTCCTGGGCGCCGCCGCAGCACCATGGGCGCC 1561 1600 CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B	(1549) (1561) (1537)	CCTGGGCTTCCTGGGCGCCGCCGCAGCACCATGGGCGCCC 1561 1600 CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431	(1549) (1561) (1537) (1561)	CCTGGGCTTCCTGGGCGCCGCCGCAGCACCATGGGCGCC 1561 1600 Consider to the control of th
Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434	(1549) (1561) (1537) (1561) (1543)	CCTGGGCTTCCTGGGCGCCGCCGCAGCACCATGGGCGCC 1561 1600 Classification of the content of the conten
Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435	(1549) (1561) (1537) (1561) (1543) (1537)	CCTGGGCTTCCTGGGCGCCGCCGCAGCACCATGGGCGCCC 1561 1600 Control of the
Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432	(1549) (1561) (1537) (1561) (1543) (1537) (1561)	CCTGGGCTTCCTGGGCGCCGCCGCCGCAGCACCATGGGCGCCC 1561 Construction of the experiment of the experimental control of t
Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B	(1549) (1561) (1537) (1561) (1543) (1537) (1561) (1561)	CCTGGGCTTCCTGGGCGCCGCCGCCGCAGCACCATGGGCGCCC 1561 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 1600 160
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FIG. 4H

71 - 400 - 14- 5404		
Ile423-Met434	(1623)	eterapotere lototranserriescrafetoriation, ese ese artesta feta ha surficio esta esqua electrició
Gln422-Tyr435	(1617)	mentioners, their statistical and was noted that of the final continuous networks and
Arg426-Lys432	(1641)	Motoralate leterate fehrusters pale in etalnic leaster minethie je leasten nictore i the
Arg426-Gly431B	(1641)	ांदर्भक्ष द्वारा विकासम्बद्धाराम द्वाराम अस्ति विकास विकास कर्म क्रिक्ट क्रिक्ट विकास विकास विकास विकास विकास
Asn425-Lys432	(1635)	Copyright in copyrights in the copyright of any analysis of the copyright
Consensus		
Consensus	(1641)	CGAGGCCCAGCAGCACCTGCTGCAGCTGACCGTGTGGGGC 1681 1720
Ile424-Ala433	(1669)	क्षेत्रका मार्थक मान्यक मन्द्रका में हिल्ला का विद्या के स्वतान क्षेत्रका कर स्वतान के स्वतान क्षेत्रका कर स्व
Trp427-Gly431	(1681)	the thronour team than the late people by the house state superviolety and the
Gln422-Tyr435B		
	(1657)	syme apprecia to the engrancist ejecteruse, edifferit eth ne editusion en english efectoris en
Arg426-Gly431	(1681)	man, any well-deposite experienced productions of interest class countries of
Ile423-Met434	(1663)	प्रवहर प्रस्तवक प्रकार ने प्रतासक्षक्षित्रक दक्षिक्र प्रताहिते होते हैं है है । विद्यान है ।
Gln422-Tyr435	(1657)	apain probleggion, in a confinctered for a low encyclinister, a for factories in
Arg426-Lys432	(1681)	रक्तरणात्रपृष्टावरम्बद्धन्तरम्बद्धनात्रम्बद्धविद्धविद्धान्त्रम् साम्यानम्बद्धान्त्रम् विद्धानान्त्रम्
Arg426-Gly431B	(1681)	का है। प्रकार में कार्यान ने लिए हो कार्यन मुंगी द्विति हो होने हैं। इस हो मुन्हरी हे ने स्वति हो से स्वति हो स
Asn425-Lys432	(1675)	कार्यक्र करिया वार्यकार विद्यात है। हो हो हो हो हो हो है
Consensus	(1681)	ATCAAGCAGCTGCAGGCCCGCGTGCTGGCCGTGGAGCGCT
	, ,	1721 1760
Ile424-Ala433	(1709)	त्य कृता, त्राच्या वा प्रवशापा, त्या प्रविधित हरूरा, कवा कृति । विधिव विधिव कृति । विविधि कृति विधिव । विव
Trp427-Gly431	(1721)	्या है। यह में
Gln422-Tyr435B	(1697)	בנות ובנות במוק בתוקבות בתבנות בו במוקבות במוקבות ביותר ביותר מוקצי אינו בנות היית בו בנות ביותר ביותר ביותר ב
Arg426-Gly431	(1721)	
Ile423-Met434		का है। भारत कार्या प्रकृतिक व्यापन के देश के अपनी कार्य के अपनी कार्य के सिंह हर्षा है है है है है है है है है
	(1703)	हरियों के प्रतिकृतिक के किए हैं कि उन्हें कि एक रिवेरिक से प्रतिकृति हैं के लिए हैं कि उन्हें कि से किए हैं कि
Gln422-Tyr435	(1697)	देशी त्रात्रात्रास्यां न्यापूर योग् स्ट्राप्टर्वेटविष्टं ब्रोध्यात्रात्रीक्षण्यात्राह्मा स्ट्रिक्त प्रवास स्ट्रिक्
Arg426-Lys432	(1721)	An enhamme tapen eine fallelig gitterheckt filosof keingebilde tionen eine
Arg426-Gly431B	(1721)	મુંગા, તારા તારાતાલામાં ભૂતિમાં ભાગમાં ભાગમાં ભાગભાગ હતા છે. જ કારાયાના ભાગમાં મોર્યા છે. જે
Asn425-Lys432	(1715)	इंग्लिक्त, महरेर के मुक्तिक प्रदेश मिल्ला मिल्ला कर्म है। यह महरे मिल्ला कर महरे मिल्ला कर मिल्ला मिल्ला है।
Consensus	(1721)	ACCTGAAGGACCAGCTGCTGGGGCATCTGGGGCTGCAG
		1761 1800
Ile424-Ala433	(1749)	ासिक १८ १५५ १५ स्ट १ महासार्व प्रतिस्था कार्या । तस्य १९६५ १५६५ १५ १५ १५ १५ १५ १५ १५ १५ १५ १५ १५ १५ १५
		द्र स्वर्ति के के क्षेत्र में भूति में के प्रतिकार के किया है। किया के किया के किया के किया के किया कि किया कि स्वरोति के किया के किया में किया कि कि
Trp427-Gly431	(1761)	Elisteles a train, me explicant, in the tester feloson, this wedge encloses an explessance of the
Trp427-Gly431 Gln422-Tyr435B	(1761) (1737)	e forester a comme provinción de la sucreción de la poés y la granción de la granción de la granción de la comme La forester a comme provinción de la commentación de la granción de la granción de la granción de la granción de
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Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434	(1761) (1737) (1761) (1743)	Electron augment for control c
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435	(1761) (1737) (1761) (1743) (1737)	Electron a comment of the profession of the prof
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432	(1761) (1737) (1761) (1743) (1737) (1761)	Elektron augmente fielden in der leiter fester des erweiten eine etwater biede in der eine der der eine der ein
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B	(1761) (1737) (1761) (1743) (1737) (1761) (1761)	Electrica activity and control activity and activity and activity and activity activity activity and activity activity and activity and activity and activity and activity activity and activity activity and activity activit
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432	(1761) (1737) (1761) (1743) (1737) (1761)	Elektron augmente fielden in der leiter fester des erweiten eine etwater biede in der eine der der eine der ein
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Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761)	EMCLES ACTION OF THE POCKSTOP ACTION IN THE PROPERTY OF SECURE ACTION OF THE POCKSTOP ACTIO
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Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761) (1789) (1801) (1777)	EMCLESS REPRESENTATION OF THE PROPERTY OF THE
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761) (1789) (1801) (1777) (1801) (1783)	EMCLESS REPRESENTATION OF THE PROPERTY OF THE
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761) (1789) (1801) (1777) (1801) (1783) (1777)	EMCLES ACTION OF THE PROCESS OF THE CONTROL OF THE PROCESS OF THE
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Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761) (1789) (1801) (1777) (1801) (1783) (1777) (1801) (1801) (1801)	Endergraphic programme of the control of the contro
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Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761) (1789) (1801) (1777) (1801) (1783) (1777) (1801) (1801) (1801) (1795)	EMCIENTACIONA CONTROLO DE CONT
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Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1755) (1761) (1789) (1801) (1777) (1801) (1777) (1801) (1801) (1795) (1801) (1801) (1829) (1841)	Entremental contract of the co
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Ile423-Met434 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1761) (1775) (1801) (1777) (1801) (1783) (1777) (1801) (1801) (1801) (1795) (1801) (1829) (1841) (1817)	EMERICAN CONTROL OF THE CONTROL OF T
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Ile423-Met434 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431B Asn425-Lys432 Consensus	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1761) (1755) (1761) (1801) (1777) (1801) (1783) (1777) (1801) (1801) (1795) (1801) (1829) (1841) (1817) (1841)	EMERGEN AND THE PROPERTY OF TH
Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Lys432 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Ile423-Met434 Gln422-Tyr435B Arg426-Gly431 Ile423-Met434 Gln422-Tyr435 Arg426-Gly431B Asn425-Lys432 Consensus Ile424-Ala433 Trp427-Gly431 Gln422-Tyr435B Arg426-Gly431B Asn425-Lys432 Consensus	(1761) (1737) (1761) (1743) (1737) (1761) (1761) (1761) (1755) (1761) (1801) (1777) (1801) (1777) (1801) (1795) (1801) (1795) (1801) (1829) (1841) (1817) (1841) (1823)	ENGLISHEN CONTROL OF THE PROPERTY OF THE PROPE
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FIG. 4I

Arg426-Lys432	(1841)	Personal and a property of the second control of the second contro
Arg426-Gly431B	(1841)	inclifere, incremental, et certaphistoles rifeleletere rife in perfect resulting to rife in to
Asn425-Lys432	(1835)	matter and offen adopted a defeating a constitution of soft in the
Consensus	(1841)	TGACCTGGATGGAGTGGGAGCGCGAGATCGACAACTACAC
	,,	1881
Ile424-Ala433	(1869)	व्यक्ष्मपुर्वात्रक्षात्रकारा व्यक्षात्रकार्वात्रक्ष्म् व्यक्ष्मात्रकार्वात्रक्षात्रकार्वात्रकार्वात्रकार्वात्रक
Trp427-Gly431	(1881)	sustantesintistic e italistitutu in mynututunintista yirin itanististici eule
Gln422-Tyr435B	(1857)	 Sports populational publicated to property in legistrates by each of the solution of the solution.
Arg426-Gly431	(1881)	astacle of seatpolomistic language excepted with instructions in this principal
Ile423-Met434	(1863)	· complete the symmetry description and the material positions of the six symptom of the symptom of the symmetry of the symmet
Gln422-Tyr435	(1857)	อริเทศเลา เพื่อเลงสำคัญการสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถสามารถ
Arg426-Lys432	(1881)	plante angles of significant stock of the second of the se
Arg426-Gly431B	(1881)	milyalinanikensitahilali akemal madamilyan virakanikeng
Asn425-Lys432	(1875)	द्राकृतकार्याक्षां मान्यकार्यः । सार्वे स्वयक्षां कृति । सार्वे स्वयक्षां सार्वे स्वयक्षां स्वयक्षिति । सार्वे
Consensus	(1881)	CAACCTGATCTACACCCTGATCGAGGAGGCCAGAACCAG
	, ,	1921 1960
Ile424-Ala433	(1909)	Stranger (Given interestablished by the second of the seco
Trp427-Gly431	(1921)	PACIETATE PROGRESS CONTRACTOR ARTON OF SOME STATE OF THE SOME SAFETY OF THE SOME SOME SOME SOME SOME SOME SOME SOM
Gln422-Tyr435B	(1897)	 Fig. powerfullscopercy specialists from sections of a powerful sections.
Arg426-Gly431	(1921)	otal sourceauseuri elysteise regen meit nitrogen meitstalekting
Ile423-Met434	(1903)	entire the contraction and a supplicable to the contraction of the con
Gln422-Tyr435	(1897)	min transpagigation of the place and transpaging the control of th
Arg426-Lys432	(1921)	Enternal Contests of the contest of the feet below of 100 to
Arg426-Gly431B	(1921)	and the state of t
Asn425-Lys432	(1915)	. Form analist their langer even the lange of the lange to the lange t
Consensus	(1921)	CAGGAGAAGAACGAGCAGGAGCTGCTGGAGCTGGACAAGT
	(,	1961 2000
Ile424-Ala433	(1949)	द्यां द्यान महित्राही का महामान विभागतिक द्यान व्यक्ति व्यक्ति हार महामान वृत्ये व्यक्ति का मान
Trp427-Gly431	(1961)	elections in the large of enclosively building and all the state of the control o
Gln422-Tyr435B	(1937)	efective arrange and countries are reserved and constructive services of the forest of the countries of the
Arg426-Gly431	(1961)	eto anticonete i cita reservadante en varian en esta en esta esta esta esta esta esta esta esta
Ile423-Met434	(1943)	denal de mante vivere i estaturar into centre distuta non casila compositati de
Gln422-Tyr435	(1937)	Driver the events of the less deep reserve in the property and property at
Arg426-Lys432	(1961)	and in the tenth of the secretarist parties for the secretaristic secret
Arg426-Gly431B	(1961)	enterior of the effort of a C. Completence and expression in any constraint (Figure 18)
Asn425-Lys432	(1955)	to a francist for expension of the expension of
Consensus	(1961)	GGGCCAGCCTGTGGAACTGGTTCGACATCAGCAAGTGGCT
33113411343	(1301)	2001 2040
Ile424-Ala433	(1989)	o are their appropries are consistent ones to a citate factorial and
Trp427-Gly431	(2001)	केरण दर किसार १९९५ के सुर-संदर्भ देश का प्रश्निकार कर कर के किसार स्वर्ध के सम्बद्ध कर स्वर्
Gln422-Tyr435B	(1977)	हरता ताहा त्याच्या राज्यात प्रशासकार यह साता वालीसम् स्थान अस्तर यह अस्तर हो अस्ता स्थित होते होते होते । अस्
Arg426-Gly431	(2001)	क्षांत कर का कर करोबर क्षेत्रकृतिकार है कर तीर किस्टर के करवार तह कर करावेदर देखें का केंद्र
Ile423-Met434	(1983)	in the increased probabilities are sensitive to the property of the first feet for the
Gln422-Tyr435	(1977)	State Committee of Exercise Bells of the Brids as the Committee of the Exercise
Arg426-Lys432	(2001)	Control of the contro
Arg426-Gly431B	(2001)	an employment de signate Marie manifestra estrat estrata en mares estrácticia, activir este de la compansión
Asn425-Lys432	(1995)	कामा कामोग्रेस नक्षण्यभूमा विभाग क्षारे मार्था । स्थापुर्वे स्था कार्या क्षारे क्षारे क्षारे स्थापुर्वे स्थाप
Consensus	(2001)	GTGGTACATCAAGATCTTCATCATGATCGTGGGCGGCCTG
	(0000)	2041 2080
Ile424-Ala433	(2029)	च्या १०१६ (१५) व्याप्त स्थापता १८ १५ म्यु स्थापता १५ १५ स्थापता १५ १५ स्थापता १५ १५ स्थापता १५ १५ स्थापता १५ १
Trp427-Gly431	(2041)	दीमानव्यक्तार १० । श्रेटाच विकास मानव्यके भेटी होता श्रीकृतक (कामाराम (अस्त्रमार अस्य क्रिकेट क्रिकेट क्रिकेट
Gln422-Tyr435B	(2017)	राजन (दान्य द्रोभाव) गरिकामके नद्दार सम्मा _ल दासने करता और (तान हा जान) गरिका । तान शत हो तान हा दासिक गर्दा की
Arg426-Gly431	(2041)	दमदारोद्योद्याः प्रमापुर्वदानकः प्रमापन्दिवनान्त्राप्तारात्राक्षेत्र अध्यान् असीमा वस्ता स्वापनान्त्रात्रात्राहरू
Ile423-Met434	(2023)	earmonethic medican charactare band the season escaperation but the season
Gln422-Tyr435	(2017)	क्षांत्र अने बहुत हर हो हो है । हर विकास मानव किरोनी हुकार प्रति हर है । इनके स्वाह कर कि सामन है है है । हर ह
Arg426-Lys432	(2041)	while with a their county he longerenther means into let steen a consiste for a last
Arg426-Gly431B	(2041)	edental feature in the research chance with the result of the estimate tenders.
	· /	FIC 41

FIG. 4J

Asn425-Lys432	(2035)	दोमलासदोद्दारास देलंदाकुर्कमतदोद्दार स्टब्स्ट्रामा स्टब्स्ट्र्रामा स्टब्स्ट्रामा स्टब्स्ट्रामा स्टब्स्ट्र्रामा स्ट
Consensus	(2041)	
		2081 2120
Ile424-Ala433	(2069)	
Trp427-Gly431	(2081)	
Gln422-Tyr435B	(2057)	
Arg426-Gly431	(2081)	यो । तत्त्रकारकारकारकारकारकारकारकारकारकारकारकारकार
Ile423-Met434	(2063)	पुरम्भ व्यक्ति त्याकृतिक वृत्ति । वृत्ति वृत्ति । वृत्ति
Gln422-Tyr435	(2057)	रहरान है है । दिए स्केट र दिन है। इस दान विकास सामान्य स्वतान है। है। एतर ने स्वतान दिन साम सहीतन है। है
Arg426-Lys432	(2081)	ंद्रवाह इंदर,दर्भ दावदिद्र दिवसी दिवदावीतिहर प्रतिवाह दिविद्री मुक्ति में दिवसी वार्ट के प्रदर्भ कर देन
Arg426-Gly431B	(2081)	Meje tekurenn, midjælegonde handrighter om ar "efta efter handstælen for til er til e
Asn425-Lys432	(2075)	भ्यानात्राः । ज्यानान् द्रांत्रां क्षात्रां व्यानान् । ज्यानान् । ज्यानान् । व्यानान् । व्यानान् । व्यानान् ।
Consensus	(2081)	ACCGCGTGCGCCAGGGCTACAGCCCCCTGAGCTTCCAGAC
T10424 N1-422	/21001	2121 2160
Ile424-Ala433	(2109)	वर्षां कारा भेरतिक विद्या करिता के के के किए हिन्दू के किए हिन्दू के किए हैं कि किए हिन्दू के किए हैं है कि कि
Trp427-Gly431 Gln422-Tyr435B	(2121)	्राहर् । भाष्यमञ्जयदेशसम्बद्धसम्बद्धसम्बद्धसम्बद्धाः
Arg426-Gly431	(2097) (2121)	कुर द्रावर । १८ वर्षा वर्षा १८ वर्षा १८ वर्षा वर्षा । १८ वर्षा १८ वर्षा १८ वर्षा १८ वर्षा १८ वर्षा १८ वर्षा १८
Ile423-Met434	(2103)	electe is investigated to observe the project and expense of the election of t
Gln422-Tyr435	(2103)	ાં જેવા લાક કરે કરામ કરવા કર્યું છે. જે જો તેમ જ જો તેમ જ જો કરવા છે. જો જો જો તેમ જ જો જો જો જો જો જો જો જો જ જો જો જ
Arg426-Lys432	(2121)	To the latest in providing a consequence of the principal of a the first providing the following of the consequence of the cons
Arg426-Gly431B	(2121)	tendran salahan teserintah salahatifi tenentirkahatekedek teletah derim
Asn425-Lys432	(2115)	and common representational foreigned for entering the relief of the rel
Consensus	(2121)	CCGCTTCCCCGCCCCCGCGCCCCGACGCCCCGAGGGC
		2161 2200
Ile424-Ala433	(2149)	જ્યાર હામદામાં વિજિલ્લા હોલ્ફા કાર્યકાર લાવ અનુ અનુ એક એની એક્સિક કર્યા
Trp427-Gly431	(2161)	्रमाण्यासम्बद्धाः स्वतिक्षां स्वतिक्षां स्वतिक्षां स्वतिक्षां स्वतिक्षां स्वतिक्षां स्वतिक्षां स्वतिक्षां स्वति
Gln422-Tyr435B	(2137)	rangle consolite supprificio los los proportios de qualitativo de los proportios de los proportios de la consolite de la conso
Arg426-Gly431	(2161)	कृष्टा न्यक्ता भाषाद्वीय ब्रुव्यक्ता संदर्भवाद मृत्याहर द्वान भाषा भाषा व्यवस्था स्थापन है।
Ile423-Met434	(2143)	कृतक है , इसका क्षेत्रप्रदानक्ष्मक दिवस्थित है बच्चा होते हैं । इसके दिवस हो । इसके हैं । इसके हैं । इसके स्था
Gln422-Tyr435	(2137)	this displayments fortheresentation expects to be the televisional exists interstate our
Arg426-Lys432	(2161)	in the restriction of regularities when the same restriction and the six
Arg426-Gly431B	(2161)	कर्तात रिकार किर्केट रहेका विदेश होती, काम खालाहा, राह्मक प्रिति विकास है। का हम्हेंक है।
Asn425-Lys432	(2155)	क एक सम्बद्धा कार्य विकास स्थापन है वर्ष हो हो है। इस एक एक एक है है कि हो है है है है है है है है है
Consensus	(2161)	ATCGAGGAGGGGGGGGGGGGGGGGGGGGGACCGCAGCA
T1-404 31-400		2201 2240
Ile424-Ala433	(2189)	
Trp427-Gly431 Gln422-Tyr435B	(2201)	ेशन किराम्यास्तरिक्तिक्षित्रे स्थानस्य व किर्माहको देशी स्थानस्य क्रिक्त विस्तरिक्ति ।
Arg426-Gly431	(2177)	in the terminate interesting dates, in the production of the extremolypersection
Ile423-Met434	(2201) (2183)	und ein ihre Mittel des Gjedes in Sejeriuren voorte dit die 11 de eeu de Gebeurg zijd de geleggie in Gjeden. Die 1888 gebeurg die 1888 gebeurg die 1888 gebeurg die 1888 gebeurg die 1888 gebeurg zijn die 1888 gebeurg die
Gln422-Tyr435	(2177)	of the transfer of the control of th
Arg426-Lys432	(2201)	and a percentage of the property of the second process of the control of the property of the second
Arg426-Gly431B	(2201)	The second state of the second
Asn425-Lys432	(2195)	to see a contrasser, or prior particles and the statement of the
Consensus	(2201)	GCCCCTGGTGCACGGCCTGCTGGCCCTGATCTGGGACGA
	,,	2241 2280
Ile424-Ala433	(2229)	ा अंतरामान्यः । स्यान्त्रेम् स्वान्त्रेत्वः स्वतंत्रे स्वतंत्रे स्वतंत्रः स्वतंत्रः स्वतंत्रः । स्वतंत्रः । स्
Trp427-Gly431	(2241)	क्षेत्रेय वर्षे में क्षेत्र महिल्य क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्षेत्र क्ष
Gln422-Tyr435B	(2217)	क्षेत्राम क्षेत्रब्रह्म प्रदेश हरू महिला हरू । क्षेत्रवर्ष साम कार्यम् वर्षा स्ट्राह्म । क्ष्युर । हर्षा स्ट्र
Arg426-Gly431	(2241)	स्कृतनार । इति देव क्षेत्रका विकास । क्षेत्रका क्षेत्रका क्षेत्रका क्षेत्रका । क्षेत्रका विकास क्षेत्रका । क्ष
Ile423-Met434	(2223)	Bu hamfachteif Lago geleich einer Ambe unbegebie ole anbligereic
Gln422-Tyr435	(2217)	स्तर । इंदरश्र विविधानितद्वां कृताहरू में द्वार विविधान में ए प्रति विवास के विविधान हो है द्वार विद्या
Arg426-Lys432	(2241)	लेकार्तरस्थान्तरस्थित्। विक्रोपुर्वा स्थानस्था । अस्ति । क्रियाः विद्याः स्थान्ति । अस्
Arg426-Gly431B	(2241)	भूषः कट्रान्तर्थे संदर्भहोत्। बेळ्नाव १९० - बार्यकः स्थानम् वार्यास्यर्थे प्रस्तर्थद्वि । इत्यावस्य ।
Asn425-Lys432	(2235)	to related a final process of the control of the policy of the control of the con
Consensus	(2241)	CCTGCGCAGCCTGTGCCTGTTCAGCTACCACCGCCTGCGC

FIG. 4K

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2281
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     2320
                                                                                                                                                                                                                                                                                            utterenkertanelendenträttetelereteneretelengthrefennatertidentelebude
                            Ile424-Ala433
                                                                                                                                                                                                        (2269)
                         Trp427-Gly431
                                                                                                                                                                                                             (2281)
                                                                                                                                                                                                                                                                                            physicia naturnologica de la feleta de la feleta de la maio de caladore e de la cidade del cidade de la cidade del cidade de la cidade del cidade del cidade de la cidade de la cidade del cidade de la cidade del cidad
              Gln422-Tyr435B
                                                                                                                                                                                                                                                                                            crate in measurable expectations to total content of the entitle problem of
                                                                                                                                                                                                        (2257)
                         Arg426-Gly431
                                                                                                                                                                                                            (2281) The tenterior elementation in the following characters and the second control of the following the second control of the 
                         Ile423-Met434
                                                                                                                                                                                                      (2263) prestuding a grant particle (configuration of prestuding
                         Gln422-Tyr435
                                                                                                                                                                                                            (2257) वंशिवादमध्यांभार्याम् विभावतिकार्याद्यां विभावतार 
                        Arg426-Lys432
                                                                                                                                                                                                            (2281)
                                                                                                                                                                                                                                                                                            ्रवेशो । विभावत्वभूतिकारोतिवस्तर्वातिवस्तर्वाति । स्वतः विभावतः विद्यानः वृद्धार्थन्ति । स्वतः विभावतः । स्वतः
             Arg426-Gly431B
                                                                                                                                                                                                                                                                                            adacte state take an evaluation for evaluation is an evaluation of experience and evaluation
                                                                                                                                                                                                          (2281)
                                                                                                                                                                                                          (2275) maken the algregious construction in endocates sparked outgroup of the position
                        Asn425-Lys432
                                                                       Consensus
                                                                                                                                                                                                         (2281) GACCTGATCCTGATCGCCGCCCGCATCGTGGAGCTGCTGG
                                                                                                                                                                                                                                                                                              2321
                        Ile424-Ala433
                                                                                                                                                                                                         (2309)
                                                                                                                                                                                                                                                                                           ार्वा संबोधित हो। या विद्यार स्वापन विद्यार स्वापन स्वापन स्वापन स्वापन स्वापन स्वापन स्वापन स्वापन स्वापन स्व
                                                                                                                                                                                                        (2321)
                      Trp427-Gly431
                                                                                                                                                                                                                                                                                          eals of the legale paged and easter the construction of the construction of the legal of the construction of the legal of the construction of the 
          Gln422-Tyr435B
                                                                                                                                                                                                        (2297)
                      Arg426-Gly431
                                                                                                                                                                                                        (2321) Constitute of the the property of the constitution of the c
                                                                                                                                                                                                         (2303) and later for his following constraint countries in the set of the set
                        Ile423-Met434
                      Gln422-Tyr435
                                                                                                                                                                                                         (2297)
                                                                                                                                                                                                                                                                                        Acres retransfelle, acretament ausgrift falls paragraph per transfellatif partities en
                    Arg426-Lys432
                                                                                                                                                                                                         (2321) melojatetetin metalienija injustrajetet ingraniteti, jenjakatetet metalianjetet in
         Arg426-Gly431B
                                                                                                                                                                                                                                                                                       who date in the limit stadestates intervestigations included
                                                                                                                                                                                                         (2321)
                    Asn425-Lys432
                                                                                                                                                                                                         (2315) वा विकास के जीव जिल्ला का वर्ष किंद्रा विकास का उपन उपनुष्ट मार्ग के महाद्वार में महाद्वार के स्थान
                                                                                                                                                                                                        (2321) GCCGCCGCGGCTGGGAGGCCCTGAAGTACTGGGGCAACCT
                                                                     Consensus
                                                                                                                                                                                                                                                                                          2361
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              2400
                                                                                                                                                                                                (2349) हर प्रायम्भाग मा मन्त्राध्या व्यक्तिमात्राक्षणं सम्बद्धिक विकास
                    Ile424-Ala433
                                                                                                                                                                                                        Trp427-Gly431
         Gln422-Tyr435B
                                                                                                                                                                                                 (2337) Warding or the miles of the following the property of t
                 Arg426-Gly431
                                                                                                                                                                                                        (2361)
                                                                                                                                                                                                                                                                                      ein mangelijanempitina mijesikinjajajanjajestanostessikas mpaktanija indatog optopistu einog
                  Ile423-Met434
                                                                                                                                                                                                      (2343) Selection deliver between the property of the factories of
                  Gln422-Tyr435
                                                                                                                                                                                                     (2337) Ch. 1911 indexperient than the professional configuration of the profession of the configuration of the con
                 Arg426-Lys432
                                                                                                                                                                                                        (2361) व्यक्ष्माराज्य स्थापनावर्षः । विवृत्तिकार्षाति विद्यविकार्यावः । विद्यानुद्रिकार्याक्षेत्रे विकास विद्यानि
                                                                                                                                                                                                     (2361) The sufficient mediate relation from the control of the con
      Arg426-Gly431B
                 Asn425-Lys432
                                                                                                                                                                                                      (2355)
                                                                                                                                                                                                                                                                                   The sea section in the control of the Application of the season of the s
                                                                                                                                                                                                    (2361) GCTGCAGTACTGGATCCAGGAGCTGAAGAACAGCGCCGTG
                                                               Consensus
                                                                                                                                                                                                                                                                                      2401
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             2440
                 Ile424-Ala433 (2389)
                                                                                                                                                                                                    (2401) 14 1
                Trp427-Gly431
     Gln422-Tyr435B
                                                                                                                                                                                                    (2377)
              Arg426-Gly431
                                                                                                                                                                                                                                                                                                                                       रेक्ट मा गाँक देश देखाँका एक क्षेत्र में क्षा के किस्सी
                                                                                                                                                                                                    (2401)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     v classicycyczją o ektorem v s
                Ile423-Met434
                                                                                                                                                                                                    (2383) Res
                                                                                                                                                                                                                                                                                                                           indeprina of other field factors in tessify any students is inferential exercises and
              Gln422-Tyr435
                                                                                                                                                                                                    (2377)
              Arg426-Lys432
                                                                                                                                                                                                    (2401) 101
                                                                                                                                                                                                                                                                                                                          Lington-golggetergiste Dans setsyettennes estrependitieke albeiteine
    Arg426-Gly431B
                                                                                                                                                                                                                                                                                                                                  न्तरंकत् प्रतानविदेशवास्तातः तत्रकातः द्वानुन्तरं वर्षाकारकेत्रार्वकारकेत्रवास्त्रवेत्रस्य विद्यान्तरं विद्या
                                                                                                                                                                                                    (2401)
              Asn425-Lys432
                                                                                                                                                                                                                                                                                    the employers of the contributed for the following specific for the followi
                                                                                                                                                                                                 (2395)
                                                             Consensus
                                                                                                                                                                                             (2401) AGCCTGTTCGACGCCATCGCCATCGCCGTGGCCGAGGGCA
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        2480
                                                                                                                                                                                                (2429) F. Will interest property and a few property of the contract of the con
              Ile424-Ala433
              Trp427-Gly431
                                                                                                                                                                                                (2441)
                                                                                                                                                                                                                                                                                ार एका मान्त्रिकेट प्रमान्त्रियोक्षेत्र कोच्यानिक्षेत्र कोच्याच्याच्याच्यानिक्ष्याक्ष्याक्ष्याक्ष्याक्ष्या एक ठाकोर
 Gln422-Tyr435B
                                                                                                                                                                                                 (2417)
                                                                                                                                                                                                                                                                                   (2441) sammaticion apprendinación in medical la mentale profeseración el mas
             Arg426-Gly431
             Ile423-Met434
                                                                                                                                                                                                 (2423) subspiral elejorate to financial engineering elejorate production to the
             Gln422-Tyr435
                                                                                                                                                                                                (2417) The state of the few angles of the state of the first of the state of the first of the few and 
             Arg426-Lys432
                                                                                                                                                                                                                                                                                        in point in the individual section in political contraction is exercise from white
                                                                                                                                                                                                 (2441)
Arg426-Gly431B
                                                                                                                                                                                                                                                                                      (2441)
                                                                                                                                                                                                (2435) व्यवस्थानिक विदेशकाल्या द्वारा स्थानिक विदेश स्थानिक 
             Asn425-Lys432
                                                            Consensus
                                                                                                                                                                                                (2441) CCGACCGCATCATCGAGGTGGCCCAGCGCATCGGCCGCGC
                                                                                                                                                                                                                                                                                2481
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     2520
                                                                                                                                                                                                (2469) CONTRACTOR CONTRACTOR OF CONTRACTOR CONTRACTOR OF C
            Ile424-Ala433
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FIG. 4L

•		
Trp427-Gly431	(2481)	cussed or kelephological adjects to be substituted by a substitute of the second
Gln422-Tyr435B	(2457)	
Arg426-Gly431	(2481)	the many had may of the parties and reference and property of the property of the property of the parties of th
Ile423-Met434	(2463)	establisació in este especial esta de la logació de la lagra de la
Gln422-Tyr435	(2457)	क्ष्माना के प्राप्त कर्मा होता है। इस क्षेत्र के क्ष्मा कर
Arg426-Lys432	(2481)	countries detectablished interest and option and electricity of the interest of the countries of the second
Arg426-Gly431B	(2481)	कार्याम् अन्यविक्रेशेल्डा प्रश्नेत्वा व्यवस्थात् । व्यवस्थात् ।
Asn425-Lys432	(2475)	contribute remediation of a strict of the Color to the property of the contribute of the contribute of the color
Consensus	(2481)	CTTCCTGCACATCCCCCGCCGCATCCGCCAGGGCTTCGAG
		2521 2541
Ile424-Ala433	(2509)	esero in le encinque de la marchia de la mar
Trp427-Gly431	(2521)	Marie reference mode i determinação resolvente.
Gln422-Tyr435B	(2497)	entally political and the material for the law de
Arg426-Gly431	(2521)	Series Color Break Action Series Color
Ile423-Met434	(2503)	thefrence of year inches who is not the
Gln422-Tyr435	(2497)	अहर क Could bring to the से सुनिक्षित के से स्ट्री
Arg426-Lys432	(2521)	tife to facility figure of the program of the control of the contr
Arg426-Gly431B	(2521)	कृष्णि को दिश्वासीकोटन संकृष्णि <u>स्त</u> ्रेष्ट्रस्था । स्ट
Asn425-Lys432	(2515)	Malajaretangalisesangantysesangarita
Consensus	(2521)	CGCGCCTGCTGTAACTCGAG

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FIG. 4M

WO 00/39303	28	/ ₁ 65 PCT/US99/31272
		1 30
Leu122-Ser199-Tryp427-G1y431	(1)	area (Carriera de la carriera del carriera de la carriera de la carriera del carriera de la carriera del la carriera de la car
Val127-Asn195-Arg426-Gly431	(1)	The Manager Manager of Table 1 and the Cartes of the Carte
Val120-Thr202-Ile424-Ala433	(1)	GAATTEGECACCATGGATGCAATGAAGAGA
Leu122-Ser199-Arg426-Lys432	(1)	GAATTCGCCACCATGGATGCAATGAAGAGA
Leu122-Ser199-Arg426-Gly431	(1)	GAATTCGCCACCATGGATGCAATGAAGAGA
Lys121-Val200-Asn425-Lys432	(1)	GAATTCGCCACCATGGATGCAATGAAGAGA
Val120-Ile201-Ile424-Ala433	(1)	Control of the Contro
Val120-Ile201B-Ile424-Ala433	(1)	and the second contract of the second contrac
Consensus	(1)	
		31 60
Leul22-Ser199-Tryp427-Gly431	(31)	 Introduct the second control of the co
Val127-Asn195-Arg426-Gly431	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
Val120-Thr202-Ile424-Ala433	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
Leu122-Ser199-Arg426-Lys432	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
Leu122-Ser199-Arg426-Gly431	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
Lys121-Val200-Asn425-Lys432	(31)	GGGCTGTGTGTGTGCTGCTGTGTGGA
Val120-Ile201-Ile424-Ala433	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
Val120-Ile201B-Ile424-Ala433	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
Consensus	(31)	GGGCTCTGCTGTGTGCTGCTGTGTGGA
		61 90
Leul22-Ser199-Tryp427-Gly431	(61)	GCAGTCTTCGTTTCGCCCAGCGCCGTGGAG
Val127-Asn195-Arg426-Gly431	(61)	GCAGTCTTCGTTTCGCCCAGCGCCGTGGAG
Val120-Thr202-Ile424-Ala433	(61)	GCAGTETTCGTTTCGCCCAGCGCCGTGGAG
Leu122-Ser199-Arg426-Lys432	(61)	GCAGTCTTCGTTTCGCCCAGCGCCCTGGAG
Leu122-Ser199-Arg426-Gly431	(61)	GCAGTCTTCGTTTCGCCCAGCGCCGTGGAG
Lys121-Val200-Asn425-Lys432	(61)	GCAGTCTTCGCCCAGCGCCGTGGAG
Val120-Ile201-Ile424-Ala433	(61)	GCAGTCTTCGTTTCGCCCAGCGCCGTGGAG
Val120-Ile201B-Ile424-Ala433	(61)	GCAGTCTTCGTTTCGCCCAGCGCCGTGGAG
Consensus	(61)	GCAGTCTTCGTTTCGCCCAGCGCCGTGGAG
		91 120
Leu122-Ser199-Tryp427-Gly431	(91)	AAGCTGTGGGTGACCGTGTACTACGGCGTG
Val127-Asn195-Arg426-Gly431	(91)	AAGCTGTGGGTGACCGTGTACTACGGCGTG
Val120-Thr202-Ile424-Ala433	(91)	AAGCTGTGGCTGACCGTGTACTACGGCGTG
Leu122-Ser199-Arg426-Lys432	(91)	AAGCTETGGGTGACCGTGTACTACGGCGTG
Leu122-Ser199-Arg426-Gly431	(91)	AAGCTGTGGGTGACCGTGTACTACGGCGTG
Lys121-Val200-Asn425-Lys432	(91)	AAGETETEGGTGACCGTGTACTACGGCGTG
Val120-Ile201-Ile424-Ala433	(91)	AAGCTGTCGCTGACCGTGTACTACGGCGTG
Val120-Ile201B-Ile424-Ala433	(91)	AAGCTGTGGGTGACCGTGTACTACGGCGTG
Consensus	(91)	AAGCTGTGGGTGACCGTGTACTACGGCGTG
		121 150
Leu122-Ser199-Tryp427-Gly431	(121)	CCCGTGTGGAAGGAGGCCACCACCACCGTG
Val127-Asn195-Arg426-Gly431	(121)	CECETETEGAAGGAGGCCACCACCETG
Val120-Thr202-Ile424-Ala433	(121)	CCCC CFCGAAGGAGGCCACCACCACCTG
Leu122-Ser199-Arg426-Lys432	(121)	essergregaaggceaccascaceetg
Leu122-Ser199-Arg426-Gly431	(121)	CCCCCCCCACCACCACCCCCCCCCCCCCCCCCCCCCCCC
Lys121-Val200-Asn425-Lys432	(121)	CECGTGTGGAGGAGGCCACCACCACCTG
Val120-Ile201-Ile424-Ala433	(121)	CCCGTGTGGAAGGAGGCCACCACCACCCTG
Val120-Ile201B-Ile424-Ala433	(121)	CCCGTGTGGAAGGAGGCCACCACCACCTG
Consensus	(121)	CCCGTGTGGAAGGAGGCCACCACCACCCTG
		151 180
Leu122-Ser199-Tryp427-Gly431	(151)	TTCTGCGCCAGCGACGCCTACGAC
Val127-Asn195-Arg426-Gly431	(151)	TTCTGCGCCAGCGACGCCTACGAC
Val120-Thr202-Ile424-Ala433	(151)	TTCTGCGCCAGCGCCAAGGCCTACGAC
Leul22-Ser199-Arg426-Lys432	(151)	TTCTGEGCCAGCGACGCCAAGGCCTACGAC
Leu122-Ser199-Arg426-Gly431	(151)	TTCTGCGCCAGCGACGCCAAGGCCTACGAC
Lys121-Val200-Asn425-Lys432	(151)	TTCTGCGCCAGCGACGCCTACGAC

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Val120-Ile201-Ile424-Ala433	(151)		CGCCAAGGCCTACGAC
Val120-Ile201B-Ile424-Ala433	(151)		ACGCCAAGGCCTACGAC
Consensus	(151)		ACGCCAAGGCCTACGAC
331.341.343	(101)	181	210
Leu122-Ser199-Tryp427-G1y431	(181)		ACGTGTGGGCCACCCAC
Val127-Asn195-Arg426-Gly431	(181)		ACGTGTGGGCCACCCAC
Val120-Thr202-Ile424-Ala433	(181)		CGTGTGGGCCACCCAC
Leu122-Ser199-Arg426-Lys432	(181)		CGTGTGGGCCACCCAC
Leu122-Ser199-Arg426-Gly431	(181)		CGTGTGGGCCACCAC
Lys121-Val200-Asn425-Lys432	(181)		CGTGTGGGCCACCCAC
Val120-Ile201-Ile424-Ala433	(181)		CGTGTGGGCCACCCAC
Val120-Ile201B-Ile424-Ala433	(181)		CGTGTGGGCCACCCAC
Consensus	(181)		CGTGTGGGCCACCCAC
		211	240
Leu122-Ser199-Tryp427-Gly431	(211)	GCCTGCGTGCCCAC	CGACCCCAACCCCCAG
Vall27-Asn195-Arg426-Gly431	(211)		CGACCCAACCCCCAG
Val120-Thr202-Ile424-Ala433	(211)		CGACCCCAACCCCCAG
Leu122-Ser199-Arg426-Lys432	(211)		CGACCCCAACCCCCAG
Leu122-Ser199-Arg426-Gly431	(211)		CGACCCCAACCCCCAG
Lys121-Va1200-Asn425-Lys432	(211)		CGACCCCAACCCCCAG
Val120-Ile201-Ile424-Ala433	(211)		CGACCCCAACCCCGAG
Val120-Ile201B-Ile424-Ala433	(211)		CGACCCCAACCCCCAG
Consensus	(211)		CGACCCCAACCCCCAG
		241	270
Leu122-Ser199-Tryp427-Gly431	(241)	GAGATCGTGCTGGA	GAACGTGACCGAGAAC
Val127-Asn195-Arg426-Gly431	(241)	GAGATCGTGCTGGA	GAACGIGACCGAGAAC
Val120-Thr202-Ile424-Ala433	(241)	GAGATCGTGCTGGA	GAACGTGACCGAGAAC
Leu122-Ser199-Arg426-Lys432	(241)		GAACGTGACCGAGAAC
Leu122-Ser199-Arg426-Gly431	(241)	GAGATOGTGCTGGA	GAACGTGACCGAGAAC
Lys121-Va1200-Asn425-Lys432	(241)		GAACGTGACCGAGAAC
Val120-Ile201-Ile424-Ala433	(241)		GAACGTGACCGAGAAC
Val120-Ile201B-Ile424-Ala433	(241)		GAACGTGACCGAGAAC
Consensus	(241)		GAACGTGACCGAGAAC
		271	300
Leu122-Ser199-Tryp427-Gly431	(271)		GAACAACATEGTEEAG
Val127-Asn195-Arg426-Gly431	(271)		gaacaacatggtegag
Val120-Thr202-Ile424-Ala433	(271)		dalam waxioo kidalo
Leu122-Ser199-Arg426-Lys432	(271)		GAACAACATISGT GIGAG
Leu122-Ser199-Arg426-Gly431	(271)		GAACAACATGGTGGAG
Lys121-Val200-Asn425-Lys432	(271)		GAACAACATGGTGGAG
Val120-Ile201-Ile424-Ala433	(271)		GAACAACATGGTGGAG
Vall20-Ile201B-Ile424-Ala433	(271)		GAACAACATGGTGGAG
Consensus	(271)		GAACAACATGGTGGAG
Tau 100 0 100 0 100		301	330
Leu122-Ser199-Tryp427-Gly431	(301)		ATCAVCAGECTIONEG
Vall27-Asn195-Arg426-Gly431	(301)	AND DESCRIPTION OF THE PROPERTY OF THE PROPERT	Tatcatcagcctgtgg
Val120-Thr202-Ile424-Ala433	(301)		EATEATCAGECT GUEG
Leu122-Ser199-Arg426-Lys432	(301)	CAGATGCACGAGGAC	CATCATCAGCCTGTGG
Leu122-Ser199-Arg426-Gly431	(301)		CATCATCAGCCTGTGG
Lys121-Val200-Asn425-Lys432 Val120-Ile201-Ile424-Ala433	(301)		CATCATCAGECTGTGG
Val120-11e201-11e424-Ala433 Val120-11e201B-11e424-Ala433	(301)		CATCATCAGCCTGTGG
	(301)		CATCATCAGECTGTGG
Consensus	(301)		CATCATCAGCCTGTGG
1.011122=Sor100-T-1-427 Cl.:421	(221)	331	360
Leu122-Ser199-Tryp427-Gly431			SCCCTGCGTGAAGCTG
Val127-Asn195-Arg426-Gly431 Val120-Thr202-Ile424-Ala433			CCCTGCGTGAAGCTG
**************************************	(331)	GACCAGAGCCTGAAG	CCCTGCGTG

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Leu122-Ser199-Arg426-Lys432	(331)	GACCAGAGCCTGAAGCCCTGCGTGAAGCT	Ġ
Leu122-Ser199-Arg426-Gly431	(331)	GACCAGAGCCTGAAGCCCTGCGTGAAGCT	
		GACCAGAGCCTGAAGCCCTGCGTGAAGCT	
Lys121-Val200-Asn425-Lys432	(331)	and a second control of the second control o	
Val120-Ile201-Ile424-Ala433	(331)	GACCAGAGCCTGAAGCCCTGCGTG	
Vall20-Ile201B-Ile424-Ala433	(331)	GACCAGAGCCTGAAGCCCTGCGTG	
Consensus	(331)	GACCAGAGCCTGAAGCCCTGCGTGAAGCT	
		361 39	0
Leu122-Ser199-Tryp427-Gly431	(361)	GG	-
Val127-Asn195-Arg426-Gly431	(361)	ACCCCCTGTGCGTGGGGGCAGGGAACTG	С
Val120-Thr202-Ile424-Ala433	(355)		-
Leu122-Ser199-Arg426-Lys432	(361)		
Leu122-Ser199-Arg426-Gly431	(361)	GG	-
Lys121-Val200-Asn425-Lys432	(357)	·	_
Val120-Ile201-Ile424-Ala433	(355)		_
/all20-Ile201B-Ile424-Ala433	(355)		
Consensus	(361)	GG	
Consensus	(301)	391 42	Λ
0.122_Carl 00_mvim 427 -Cl +421	(363)	CAACAGCGTGATCACCCAGGCCTGCCC	
Leu122-Ser199-Tryp427-Gly431			
Val127-Asn195-Arg426-Gly431	(391)	AACACCAGGCTGATCACCCAGGCCTGCCC	
Val120-Thr202-Ile424-Ala433	(357)	CGGGCCACCCAGGCCTGCCC	
Leu122-Ser199-Arg426-Lys432	(363)	CAACAGEGTGATCACCCAGGCCTGCCC	
Leul22-Ser199-Arg426-Gly431	(363)	CAACAGCGTGATCACCCAGGCCTGCCC	
Lys121-Val200-Asn425-Lys432	(359)	CCCCCGTGATCACCCAGGCCTGCCC	
Val120-Ile201-Ile424-Ala433	(355)	GEGGCATCACCCAGGCCTGCCC	С
/al120-Ile201B-Ile424-Ala433	(355)	CCCGGCATCACCCAGGCCTGCCC	Ć
Consensus	(391)	CA CAGCGTGATCACCCAGGCCTGCCC	С
•		421 45	0
Leu122-Ser199-Tryp427-Gly431	(391)	AAGGTGAGETTCGAGCCCATCCCATCCA	C
Val127-Asn195-Arg426-Gly431	(421)	AAGGTEAGETTEGAGCCCATCCCCATCCA	
Val120-Thr202-Ile424-Ala433	(379)	AAGGTGAGOTTCGAGCCCATCCCATCCA	
Leu122-Ser199-Arg426-Lys432	(391)	AAGGTEAGCTTEGAGCCCATCCCATCCA	
Leu122-Ser199-Arg426-Gly431	(391)	AAGGTGAGCTTEGAGCCCATCCCCATCCA	
	(385)	AAGGTGAGCTTCGAGCCCATCCCCATCCA	Τ.
Lys121-Val200-Asn425-Lys432			
Val120-Ile201-Ile424-Ala433	(379)	Avaggije a 500 a cocagoco an ooco an coa	
/all20-Ile201B-Ile424-Ala433	(379)		
Consensus	(421)		
		451 48	
Leu122-Ser199-Tryp427-Gly431	(421)		
Val127-Asn195-Arg426-Gly431	(451)		
Val120-Thr202-Ile424-Ala433	(409)	TACHECOCOLOGGCTTCGCCATCCT	G
Leu122-Ser199-Arg426-Lys432	(421)	PACCECCCCCCCCCCCTTCCCCATCCT	G
Leu122-Ser199-Arg426-Gly431	(421)	NAME LE COMPANION DE LA COMPAN	Ģ
Lys121-Val200-Asn425-Lys432		୵ୡ୵ୡ୵ୡୠଌ୷୷ୡଢ଼୕ଢ଼ <mark>ୢଌ୕ଌୄଌ</mark>	Ġ
Val120-Ile201-Ile424-Ala433	(409)		G
/al120-11e201-11e424-Ala433	(409)	PACHEGES SE SECEGETTE GEGATEST	
Consensus	(451)	TACTGCGCCCCGCCGGCTTCGCCATCCT	
Consensus	(471)	481 51	
100 0100	/ 4 = 1 \	AAGTGCAAGGACAAGAAGTTCAACGGCAG	
Leu122-Ser199-Tryp427-Gly431			
Val127-Asn195-Arg426-Gly431	(481)	AAG (GEAAGGACAAGAAGTTEAACGGCAG	
Val120-Thr202-Ile424-Ala433	(439)		
Leul22-Ser199-Arg426-Lys432	(451)		
Leul22-Ser199-Arg426-Gly431		AAGTGLAACGACAAGAAGTTCAACGGCAG	
Lys121-Val200-Asn425-Lys432	(445)	AAGTGCAACGACAAGAAGTTCAACGGCAG	
	11201	AAGTGCAACGACAAGAAGTTCAACGGCAG	C
Vall20-Ile201-Ile424-Ala433	(439)		
	(439)	B. Carrier and Control of the Contro	
Val120-Ile201-Ile424-Ala433		AAGTGCAACGACAAGAAGTTCAACGGCAG	C

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Leu122-Ser199-Tryp427-Gly431	.31 (481)	GGGGGGGACCAACGTGAGCACCGTGGAG
Val127-Asn195-Arg426-Gly431	(511)	GGCCCTGCACCAACGTGAGCACCGTGCAG
Val120-Thr202-Ile424-Ala433	(469)	GGCCCCTGCACCAACGTGAGCACCGTGCAG
Leu122-Ser199-Arg426-Lys432	(481)	GGCCCCTGCACCAACGTGAGCACCGTGCAG
Leu122-Ser199-Arg426-Gly431	(481)	GGCCCTGCACCAACGTGAGCACCGTGCAG
Lys121-Val200-Asn425-Lys432	(475)	GGCCCCTGCACCAACGTGAGCACCGTGCAG
Val120-Ile201-Ile424-Ala433	(469)	GGCCCCTGCACCAACGTGAGCACCGTGCAG
Val120-Ile201B-Ile424-Ala433	(469)	GGCCCTGCACCAACGTGAGCACCGTGCAG
Consensus	(511)	GGCCCCTGCACCAACGTGAGCACCGTGCAG
	,,	541 570
Leu122-Ser199-Tryp427-Gly431	(511)	TGCACCCACGCCATCCGCCCCGTGGTGAGC
Val127-Asn195-Arg426-Gly431	(541)	TGCACCCACGCCATCCGCCCCGTGGTGAGC
Val120-Thr202-Ile424-Ala433	(499)	TGCACCCACGCCATCCGCCCCGTGGTGAGC
Leu122-Ser199-Arg426-Lys432	(511)	TGCACCCACGGCATCCGCCCCGTGCTGAGC
Leu122-Ser199-Arg426-Gly431	(511)	TGCACCCACGGCATCCGCCCCGTGGTGAGC
Lys121-Val200-Asn425-Lys432	(505)	TGCACCCACGCCATCCGCCCCGTGGTGAGC
Val120-Ile201-Ile424-Ala433	(499)	TGCACCCACGCCATCCGCCCCCGTGGTGAGC
Val120-Ile201B-Ile424-Ala433	(499)	TGCACCCACGCCATCCCCCCCGTGGTGAGC
Consensus	(541)	TGCACCCACGGCATCCGCCCCGTGGTGAGC
		571 600
Leu122-Ser199-Tryp427-Gly431	(541)	ACCCAGCTGCTGCTGAACGGCAGCCTCGCC
Val127-Asn195-Arg426-Gly431	(571)	ACCCAGCTGGTGCTGAACGGCAGGCTGGCC
Val120-Thr202-Ile424-Ala433	(529)	ACCEAGCTGGTGGTGAACGGCAGCCTGGCC
Leu122-Ser199-Arg426-Lys432	(541)	ACCCAGCTGCTGCAGCGCGCCCGGCC
Leu122-Ser199-Arg426-Gly431	(541)	ACCEAGCTGCTGCTGAACGGCAGCCTGGCC
Lys121-Val200-Asn425-Lys432	(535)	ACCEAGETGETGAACGGEAGCETGGEC
Val120-Ile201-Ile424-Ala433	(529)	ACCCAGCTGCTGCTGAACGCCAGCCTGGCC
Val120-Ile201B-Ile424-Ala433	(529)	ACCCAGCTGCTGCAACGCCAGCCTGGCC
Consensus	(571)	ACCCAGCTGCTGCAACGGCAGCCTGGCC
		601 630
Leul22-Ser199-Tryp427-Gly431	(571)	GAGGAGGGCGTGGTGATCCGCAGCGAGAAC
Val127-Asn195-Arg426-Gly431	(601)	GAGGAGGCGTGGTGATCCGCAGCGAGAAC
Val120-Thr202-Ile424-Ala433	(559)	GAGGAGGGGEGAGGGAGGAGG
Leu122-Ser199-Arg426-Lys432	(571)	Garanted of the control of the contr
Leul22-Ser199-Arg426-Gly431	(571)	GAGGAGGGGGGGGGAGAAC
Lys121-Va1200-Asn425-Lys432	(565)	GAGGAGGEGETGCTGATCCGCAGGGAGAAC
Vall20-Ile201-Ile424-Ala433	(559)	GIGGIAGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
Vall20-Ile201B-Ile424-Ala433	(559)	GAGGAGGECGAGTGATCCGCAGCGAGAAC
Consensus	(601)	GAGGAGGCGTGGTGATCCGCAGCGAGAAC
		631 660
Leu122-Ser199-Tryp427-Gly431	(601)	TTCACEGACAACGCCAAGACCATCATCGTG
Val127-Asn195-Arg426-Gly431	(631)	TTCACCGACAACGCCAAGACCATCATCGTG
Val120-Thr202-Ile424-Ala433	(589)	TICACCGACAACGCCAAGACCATCATOTTG
Leu122-Ser199-Arg426-Lys432	(601)	T. CASEGACAASGECAAGACCATCATCGTG
Leul22-Ser199-Arg426-Gly431	(601)	TEACCESCAACGCCAAGACCATEATUETG
Lys121-Val200-Asn425-Lys432	(595)	TUGA GEAGA REGGGA AGA COAHEATUGEG
Val120-Ile201-Ile424-Ala433	(589)	DESCRIPTION OF THE PROPERTY OF THE COME.
Val120-Ile201B-Ile424-Ala433	(589)	TTCACCGACAACGCCAAGACCATCATCGTG
Consensus	(631)	TTCACCGACAACGCCAAGACCATCATCGTG
1100 0 100 - 100		661 690
Leul22-Ser199-Tryp427-Gly431	(631)	CAGCTGAAGGAGAGCGTGGAGATCAACTGC
Val127-Asn195-Arg426-Gly431	··(661)	CAGCTGAAGGAGAGCGTGGAGATCAACTGC
Val120-Thr202-Ile424-Ala433	(619)	CAGCTGAAGGAGAGCGTGGAGATCAACTGC
Leu122-Ser199-Arg426-Lys432	(631)	CAGCTGAAGGAGAGCGTGGAGATCAACTGC
Leu122-Ser199-Arg426-Gly431	(631)	CAGCTGAAGCAGAGCGTGGAGATCAACTGC
Lys121-Val200-Asn425-Lys432	(625)	CAGCTGAAGGAGAGCGTGGAGATCAACTGC
Val120-Ile201-Ile424-Ala433	(619)	CAGCTGAAGGAGAGCGTGGAGATCAACTGC

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Val12U-11e2U1B-11e424-Ala433	(619)	
Consensus	(661)	The state of the s
	, ,	691 720
Leu122-Ser199-Tryp427-Gly431	(661)	ACCCGCCCAACAACAACACCCGCAAGAGC
Val127-Asn195-Arg426-Gly431	(691)	ACCCGCCCAACAACAACACCCGCAAGAGC
Val120-Thr202-Ile424-Ala433	(649)	ACCCGCCCAACAACACCCCGCAAGAGC
Leu122-Ser199-Arg426-Lys432	(661)	ACCCGCCCAACAACAACACCCGCAAGAGC
Leu122-Ser199-Arg426-Gly431	(661)	ACCCGCCCAACAACACACCCGCAAGAGC
Lys121-Va1200-Asn425-Lys432	(655)	ACCEGCCCAACAACAACACCCGCAAGAGC
Val120-Ile201-Ile424-Ala433	(649)	ACCCGCCCAACAACAACACCCGCAAGAGC
Val120-Ile201B-Ile424-Ala433	(649)	ACCCGCCCAACAACAACACCCGCAAGAGC
Consensus	(691)	ACCCGCCCAACAACAACACCCGCAAGAGC
		721 750
Leu122-Ser199-Tryp427-Gly431	(691)	ATCACCATEGGECCEGGCCGCCCTTCTAC
Val127-Asn195-Arg426-Gly431	(721)	ATCACCATCGGCCCGGCCGCCCTTCTAC
Val120-Thr202-Ile424-Ala433	(679)	ATCACCATCGGCCCGGCCGCCCTTGTAC
Leu122-Ser199-Arg426-Lys432	(691)	ATCACCATCGGCCCCGGCCGCCCTTCTAC
Leu122-Ser199-Arg426-Gly431	(691)	ATCACCATCGGCCCCGGCCGCCCTTCTAC
Lys121-Va1200-Asn425-Lys432	(685)	ATCACCATCGGCCCCGGCCGCCCTTCTAC
Val120-Ile201-Ile424-Ala433	(679)	ATCACCATCGGCCCGGCCGCCCTTCTAC
Val120-Ile201B-Ile424-Ala433	(679)	ATCACCATEGGCCCCGGCCGCCCTTCTAC
Consensus	(721)	ATCACCATCGGCCCGGCCGCCCTTCTAC
		751 780
Leu122-Ser199-Tryp427-Gly431	(721)	GCCACCGCCACATCATCGCCGACATCCGC
Val127-Asn195-Arg426-Gly431	(751)	GECACCEGCGACATCATCGGCGACATCCGC
Val120-Thr202-Ile424-Ala433	(709)	GECACEGEGACATCATEGGCGACATEEGC
Leu122-Ser199-Arg426-Lys432	(721)	GCCACCGGCGACATCATCGGCGACATCCGC
Leu122-Ser199-Arg426-Gly431	(721)	GCCACCGGCGACATCATCGGCGACATCCGC
Lys121-Val200-Asn425-Lys432	(715)	GCCACEGCGACATCATEGGCGACATCEGC
Val120-Ile201-Ile424-Ala433	(709)	GCCACGGCGACATCATCGGCGACATCCGC
Vall20-Ile201B-Ile424-Ala433	(709)	GCCACCGGCGACATCATCGGCGACATCGGC
Consensus	(751)	GCCACCGGCGACATCATCGGCGACATCCGC
Tau 122 Cau 100 B 407 C 421		781 810
Leu122-Ser199-Tryp427-Gly431	(751)	CAGGOCCACTGCAACATCAGCGGGGGGAGAAG
Val127-Asn195-Arg426-Gly431	(781)	CAGGCCCACTGCAACATCAGCGGCGAGAAG
Val120-Thr202-Ile424-Ala433	(739)	<u>CAGGS COACHIGGAACATICAGCGGGGAGAAG</u>
Leu122-Ser199-Arg426-Lys432	(751)	eAGG@@@xtgraceAy.@xy.ceAEGGEGEXEXX.G
Leu122-Ser199-Arg426-Gly431 Lys121-Val200-Asn425-Lys432	(751)	CAGGGCCATERGEAACARCAGCGCGAGAAG
Vall20-Ile201-Ile424-Ala433	(745)	CAGGE CACTGCAACATCAGCGGCGAGAAG
Val120-11e201-11e424-Ala433 Val120-11e201B-11e424-Ala433	(739)	CAGGCCCACTGCAACATCAGCGGCGAGAAG
	(739)	CAGGGGCACTGCAACATCAGCGGCGAGAAG
Consensus	(781)	CAGGCCCACTGCAACATCAGCGGCGAGAAG 811 840
Leu122-Ser199-Tryp427-Gly431	(781)	811 840 TGGALCAGECTGAAGCAGATCGTGACC
Val127-Asn195-Arg426-Gly431	(811)	TGEARCACCCTGAAGCAGATCGTGACC
Val120-Thr202-Ile424-Ala433	(769)	TGGAACACACCTGAAGCAGATCGTGACC
Leu122-Ser199-Arg426-Lys432	(781)	TGGALAACACCCTGAAGCAGATCGTGACC
Leu122-Ser199-Arg426-Gly431	(781)	TGGAACACCCTGAAGCAGATCGTGACC
Lys121-Val200-Asn425-Lys432	(775)	TGGAACACCCTGAAGCAGATCGTGACC TGGAACACCCTGAAGCAGATCGTGACC
Vall20-Ile201-Ile424-Ala433	(769)	TGGAACACCCTGAAGCAGATCGTGACC
Val120-Ile201B-Ile424-Ala433	(769)	TGGAACACCCTGAAGCAGATCGTGACC
Consensus	(811)	TGGAACACCCTGAAGCAGATCGTGACC
Consendus	(011)	841 870
Leu122-Ser199-Tryp427-Gly431	(811)	AAGCTGCAGGCCCAGTTCGGCAACAAGACC
Val127-Asn195-Arg426-Gly431		ANGCIGOAGGCCCAGIICGGCAACAAGACC ANGCIGCAGGCCCAGIICGGCAACAAGACC
Val120-Thr202-Ile424-Ala433		AACCTCCAGGCCCAGTTCGGCAACAAGACC
Leu122-Ser199-Arg426-Lys432		AAGCTGCAGGCCCAGTTCGGCAACAAGACC
001133 A19420-Dy3432	(011)	<u> Guarana de Cenarir can cuuchii diice</u>

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Leu122-Ser199-Arg426-Gly431	(811)	AAGCTGCAGGCCCAGTTCGGCAACAAGACC
Lys121-Val200-Asn425-Lys432	(805)	AAGCTGCAGGCCAGTTCGGCAACAAGACC
Val120-Ile201-Ile424-Ala433	(799)	AAGCTGCAGGCCCAGTTCGGCAACAAGACC
Val120-Ile201B-Ile424-Ala433	(799)	AAGCTGCAGGCCAGTTCGGCAACAAGACC
Consensus	(841)	AAGCTGCAGGCCCAGTTCGGCAACAGACC 871 900
Leu122-Ser199-Tryp427-Gly431	(841)	871 900 ATCGTGTTCAAGCAGAGCAGCGGCGGCGAC
Val127-Asn195-Arg426-Gly431	(871)	ATCGTGTTCAAGCAGAGCAGCGGCGGCGAC
Val120-Thr202-Ile424-Ala433	(829)	ATCGTETTCAAGCAGAGCAGCGGCGGCGAC
Leul22-Ser199-Arg426-Lys432	(841)	ATCGTGTTCAAGCAGAGCAGCGGCGAC
Leu122-Ser199-Arg426-Gly431	(841)	ATCGTGTTCAAGCAGAGCAGCGGCGGCGAC
Lys121-Va1200-Asn425-Lys432	(835)	ATCGTGTTCAAGCAGAGCAGCGGCGGCGAC
Vall20-Ile201-Ile424-Ala433	(829)	ATCGTGTTCAAGCAGCAGCGGCGGCGAC
Val120-Ile201B-Ile424-Ala433	(829)	ATCGTGTTCAAGCAGAGCAGCGGCGAC
Consensus	(871)	ATCGTGTTCAAGCAGAGCAGCGGCGGCGAC
Leul22-Ser199-Tryp427-Gly431	/071\	901 930
Val127-Asn195-Arg426-Gly431	(871) (901)	CCCGAGATCGTGATGCACAGCTTCAACTGC
Vall20-Thr202-Ile424-Ala433	(859)	CCCGAGATCGTGATGCACAGCTTCAACTGC CCCGAGATCGTGATGCACAGCTTCAACTGC
Leu122-Ser199-Arg426-Lys432	(871)	CCCGACATCGTGATGCACAGCTTCAACTGC
Leu122-Ser199-Arg426-Gly431	(871)	CCCGAGATCGTGATGCACAGCTTCAACTGC
Lys121-Val200-Asn425-Lys432	(865)	CCGGAGATCGTGATGCACAGETTCAAGTGC
Val120-Ile201-Ile424-Ala433	(859)	CCCGAGATCGTGATGCACAGCTTGAACTGC
Val120-Ile201B-Ile424-Ala433	(859)	CCCGAGATCGTGATGCACAGCTTCAACTGC
Consensus	(901)	CCCGAGATCGTGATGCACAGCTTCAACTGC
V. 100 0 100		931 960
Leu122-Ser199-Tryp427-Gly431	(901)	GGCGGCGAGTTCTTCTACTGCAACAGCACC
Vall27-Asn195-Arg426-Gly431 Vall20-Thr202-Ile424-Ala433	(931) (889)	GGCGGCGAGTTCTTCTACTGCAACAGCACC
Leu122-Ser199-Arg426-Lys432	(901)	GGCGGGGAGTTCTTCTACTGCAACAGCACC GGCGGGGAGTTCTTCTACTGCAACAGCACC
Leu122-Ser199-Arg426-Gly431	(901)	GGCGGGAGTTCTTCTACTGCAACAGGACC
Lys121-Val200-Asn425-Lys432	(895)	GGEGGEGAGTTETTCTACTGCAACAGCACC
Val120-Ile201-Ile424-Ala433	(889)	GG@GGGACHUO!!YC!!AC!!GC!AC!!GCACC
Val120-Ile201B-Ile424-Ala433	(889)	CCGCCC (Crystes interinters CoV(G)(Cs)/9C
Consensus	(931)	GGCGGCGAGTTCTTCTACTGCAACAGCACC
		961 990
Leul22-Ser199-Tryp427-Gly431	(931)	CAGC (CONTRACACGACC) CGAACAACACC
Val127-Asn195-Arg426-Gly431	(961)	CAGCITYLTCAACAGCACCTGGAACAACACC
Val120-Thr202-Ile424-Ala433	(919)	CAGCTETTCAACAGCACCTGGAACAACACC
Leu122-Ser199-Arg426-Lys432 Leu122-Ser199-Arg426-Gly431	(931)	CAGCIGITCAACAGGACCTGGAACAACACC
Lys121-Val200-Asn425-Lys432		CAGCTETTCAACAGCACCTGGAACAACACCC CAGCTETTCAACAGCACGTGGAACAACACC
Val120-Ile201-Ile424-Ala433		CACCIGITETACACACCTGGAACACACC
Val120-Ile201B-Ile424-Ala433		GACOUS HOWAS ACOUNCE CONTINUES CONTI
Consensus		CAGCTGTTCAACAGCACCTGGAACAACACC
		991 1020
Leu122-Ser199-Tryp427-Gly431	(961)	AT CGC CCCAACACACCAACGGCACCATC
Val127-Asn195-Arg426-Gly431		ATCGGCCCAACAACACCAACGGCACCATC
Val120-Thr202-Ile424-Ala433	(949)	ATCGGCCCAACACACCAACGGCACCATC
Leu122-Ser199-Arg426-Lys432		ATCGGCCCAACAACACCAACGGCACCATC
Leu122-Ser199-Arg426-Gly431 Lys121-Val200-Asn425-Lys432		ATCGGCCCAACAACACCAACGGCACCATC
Vall20-Ile201-Ile424-Ala433		ATCGGCCCAACAACAACGGCACGATC
Val120-Ile201B-Ile424-Ala433		ATCGGCCCAACAACACCAACGGCACCATC ATCGGCCCCAACAACACCAACGGCACCATC
Consensus	•	ATCGGCCCCAACACACCAACGCACCATC ATCGGCCCCAACACACCAACGCCACCATC
00.130.1343		1021 1050
Leu122-Ser199-Tryp427-Gly431		ACCTGCCCTGCCGCATCAAGCAGATCATC
	•	A series and appropriate the series of the s

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Val127-Asn195-Arg426-Gly431
                                                      (1021) ACCCTGCCCTGCCGCATCAAGCAGATCATC
  Val120-Thr202-Ile424-Ala433
                                                       (979) ACCCTGCCCTGCCGCATCAAGCAGATCATC
  Leu122-Ser199-Arg426-Lys432
                                                       (991) ACCCTGCCCTGCCGCATCAGCAGATCATC
  Leu122-Ser199-Arg426-Gly431
                                                       (991) ACCCTGCCTGCCGCATCAAGCAGATCATC
                                                       (985) ACCCTGCCTGCCGCATCAAGCAGATCATC
  Lys121-Val200-Asn425-Lys432
  Val120-Ile201-Ile424-Ala433
                                                       (979) ACCCTGCCCTGCCGCATCAAGCAGATCATC
 Val120-Ile201B-Ile424-Ala433
                                                       (979) ACCCTGCCCTGCCGCATCAAGCAGATCATC
                                  Consensus
                                                     (1021) ACCCTGCCCTGCCGCATCAAGCAGATCATC
                                                                  1051
 Leu122-Ser199 Tryp427-Gly431
                                                      (1021) AACCGCTGGGGCGCAAGGCCATGTACGCC
  Val127-Asn195-Arg426-Gly431
                                                      (1051) AACCGCGCGCGCGCAAGGCCATGTACGCC
  Val120-Thr202-Ile424-Ala433
                                                     (1009) -----GCGGGG---GCCATGTACGCC
                                                      (1021) AACCGCGCCGCCAACAAGGCCATGTACGCC
  Leu122-Ser199-Arg426-Lys432
                                                      (1021) AACCGCGGCAGCGGCAAGGCCATGTACGCC
  Leu122-Ser199-Arg426-Gly431
                                                      (1015) AAC-----GCCCCCAAGGCCATGTAGGCC
  Lys121-Val200-Asn425-Lys432
  Val120-Ile201-Ile424-Ala433
                                                      (1009)
                                                                -----GGCGGC---GCCATGTAGGCC
                                                     (1009) ------GCGGC---GCCATGTACGCC
 Val120-Ile201B-Ile424-Ala433
                                                     (1051) AACCGC G GGCGGCAAGGCCATGTACGCC
                                  Consensus
                                                                 1081
                                                     (1051) CCCCCCATCCGCGCCCAGATCCGCTGCAGC (1081) CCCCCCATCCGCGCGCCAGATCCGCTGCAGC
Leu122-Ser199 Tryp427-Gly431
  Val127-Asn195-Arg426-Gly431
                                                     (1027) CCCC CATICOGCGCCAGA CCGC GCAGC
  Val120-Thr202-Ile424-Ala433
                                                     (1051) CCCCCATCCGCGGCAGATGCGCTGCAGC
  Leu122-Ser199-Arg426-Lys432
                                                     (1051) CCCCCCATCCGCGGCCAGATCCGCTGCAGC
  Leu122-Ser199-Arg426-Gly431
                                                     (1039) CCCCEATECGCGGCAGATCCGGTGCAGC (1027) CCCCCCATCCGCGCCAGATCCGCTGCAGC
  Lys121-Val200-Asn425-Lys432
  Val120-Ile201-Ile424-Ala433
                                                     (1027) CCCCCCATCCGCGGCCAGATCCGCTGCAGC
Val120-Ile201B-Ile424-Ala433
                                                     (1081) CCCCCCATCCGCGGCCAGATCCGCTGCAGC
                                 Consensus
                                                                 1111
                                                                                                              1140
                                                     (1081) AGCAACATEACCGGCCTGCTGCTGACCCGC
Leu122-Ser199 Tryp427-Gly431
                                                     (1111) AGCAACATGACCGGCCTGCTGACCCGC
  Val127-Asn195-Arg426-Gly431
                                                     (1057) AGCANG PROACEGGGG PECKED COLORS
  Val120-Thr202-Ile424-Ala433
                                                     (1081) AGMAN CONTROL OF CONTROL O
  Leu122-Ser199-Arg426-Lys432
 Leu122-Ser199-Arg426-Gly431
                                                     (1081) AGENTEAVEGECETE TECTENCEEEC
                                                                 AGCAVACAVIE ACCEGECTICO (COTTOA COCEC
  Lys121-Val200-Asn425-Lys432
                                                     (1069)
  Val120-Ile201-Ile424-Ala433
                                                     (1057)
                                                                 ्रित्कः, ४११७६, ४४१७%, १८व्यति देव विश्वेष्टा विश्वेष्ट विश्वेष्ट विश्वेष्ट
Val120-Ile201B-Ile424-Ala433
                                                     (1057) ACOMO CAR CONCEGNOR CONTROL OF CONCE
                                 Consensus
                                                     (1111) AGCAACATCACCGGCCTGCTGCTGACCCGC
                                                                                                              1170
Leu122-Ser199 Tryp427-Gly431
                                                     (1111) GASGGGGGSAAGAGAGAGAGAGAGACACC
                                                                 चर्चात्रस्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य
स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य
  Val127-Asn195-Arg426-Gly431
                                                     (1141)
                                                     (1087)
 Val120-Thr202-Ile424-Ala433
                                                     (1111) PARECECE INCEMENTAL CONTROL OF THE
 Leu122-Ser199-Arg426-Lys432
                                                                 EJ/MELCOCE CHATCHENTIC MICHALL MICHELLE
 Leu122-Ser199-Arg426-Gly431
                                                     (11111)
 Lys121-Val200-Asn425-Lys432
                                                     (1099)
                                                                 GYACE GEGYA/EGYGYANAYA GAYAC
 Val120-Ile201-Ile424-Ala433
                                                     (1087)
                                                                 GAGGGGGGGATAGGAGTATEAGGAAGACEAGC
                                                     (1087) GACGGCGGCAAGGAGATCAGCACCACC
Val120-Ile201B-Ile424-Ala433
                                 Consensus
                                                    (1141) GACGGCGGCAAGGAGATCAGCAACACCACC
                                                     (1141) GAGATCTTCCGCCCCGGCGGCGGCGACATG
Leu122-Ser199 Tryp427-Gly431
                                                                 GAGAYOTTECGCCCCGGCGGCGGCGACATG
 Val127-Asn195-Arg426-Gly431
                                                     (1171)
                                                                 GAGATOTTCCGCCCGGCGGCGGCGACATG
 Val120-Thr202-Ile424-Ala433
                                                     (1117)
                                                                 GAGATETTEEGCCCEGGEGGEGGCGACATG
 Leu122-Ser199-Arg426-Lys432
                                                     (1141)
                                                                 GAGATETTEESCECCGGCGGGGGGGACATG
                                                     (1141)
 Leu122-Ser199-Arg426-Gly431
 Lys121-Val200-Asn425-Lys432
                                                     (1129)
                                                                 GAGATETTEEGCCCCGGCGCGCGCGACATG
 Val120-Ile201-Ile424-Ala433
                                                     (1117)
                                                                GAGATETTICEGCCCGGCGGCGGCGACATG
Val120-Ile201B-Ile424-Ala433
                                                    (1117) GAGATICATECGECCCGGCGGCGCGCGACATG
```

Consensus	(1171)	GAGATCTTCCGCCCCGGCGGCGGCGACATG
Tav. 100 0 - 100 m - 407 m		1201 1230
Leu122-Ser199 Tryp427-Gly431	(1171)	aced expension conferences (cody conferences)
Val127-Asn195-Arg426-Gly431	(1201)	CC-PAGNATIC GOOGLAGGE GAGGERS AND AND
Vall20-Thr202-Ile424-Ala433	(1147)	CONTRACTOR CHICAGOTORICAN
Leu122-Ser199-Arg426-Lys432	(1171)	SESEMENTAL COSCINE CONTROL OF THE PROPERTY OF THE
Leu122-Ser199-Arg426-Gly431	(1171)	Chical transfer controls control to the
Lys121-Val200-Asn425-Lys432	(1159)	CACCOLARCEGUCGOAGOGGCCCCCCADARC
Val120-Ile201-Ile424-Ala433	(1147)	CSCSACARCIGGESCAGCEAGCECTACARA
Vall20-Ile201B-Ile424-Ala433	(1147)	COMBINATORS COACGEAG TOTAL AND
Consensus	(1201)	CGCGACAACTGGCGCGCGAGCTGTACAAG
Toul 22 - Som 100 Mm - m 427 Cl - 421	(1201)	1231 1260
Leu122-Ser199 Tryp427-Gly431	(1201)	DACAAGG TOG GAAGA TOG AGS CCC EGGC
Val127-Asn195-Arg426-Gly431	(1231)	TACARCEICCECARCATECHCOCONCEC
Val120-Thr202-Ile424-Ala433	(1177)	TATANGGIGGIGGIGGATIGANGGIGGIGGIGG
Leu122-Ser199-Arg426-Lys432	(1201)	TACHAGGIGGIONACATEGAECUSCIGGGO
Leu122-Ser199-Arg426-Gly431	(1201)	TACANGETISTIGNANAT CONSCICTINGGC
Lys121-Val200-Asn425-Lys432	(1189)	FACAAGGTEGICAACATCGAGCCCCTGGGC
Val120-Ile201-Ile424-Ala433	(1177)	TACAAGG OF TGAAGATO CAGCECCTIGGGG
Val120-Ile201B-Ile424-Ala433	(1177)	TACAAGGIGDEGAAGATLGAGCCCCTODGC
Consensus	(1231)	TACAAGGTGGTGAAGATCGAGCCCCTGGGC
Leu122-Ser199 Tryp427-Gly431	(1231)	1261 1290
Val127-Asn195-Arg426-Gly431	(1251)	GTGGGGGGBGGAAGGCGAAGCGGGGCCGTG
Val120-Thr202-Ile424-Ala433	(1201)	GTGSCCCCGGCCAAGGCCAAGGCCCGCCGG
Leu122-Ser199-Arg426-Lys432	(1231)	GREGOCCCOACCAAGECCAAGEGCELECETG
Leu122-Ser199-Arg426-Gly431	-	GTGGCCCC RCCAAGGCCAAGCGCCGCTGG
Lys121-Val200-Asn425-Lys432	(1231)	GIGGCCCCAGCAAGCCAAGCGCCGCGTG
Vall20-Ile201-Ile424-Ala433	(1219)	GTGGCCCGCACCAAGCCCCGCGTG
Val120-I1e2018-I1e424-Ala433	(1207)	GTGGCCCCLACCAMGGCCAAGCGCCGCGTG
	(1207) (1261)	STGGCCCCACCAAGCCCAAGCCCCCCCCCC
Consensus	(1201)	GTGGCCCCCACCAAGGCCCAAGCGCCGCGTG 1291 1320
Leu122-Ser199 Tryp427-Gly431	(1261)	1320
Val127-Asn195-Arg426-Gly431	(1291)	GTGCAGCGCGAGAAGCGCGCGTGACCCTG
Val120-Thr202-Ile424-Ala433	(1231) (1237)	GTGTAECGLEAGAAGCECECTETGACCCTC
Leul22-Ser199-Arg426-Lys432	(1261)	STGCAGCGCCAGATICO E DECONTRA O CATO
	,	GTGCAGCGCCAGTAGCGCGCCGTCACCDTG
Leul22-Ser199-Arg426-Gly431 Lys121-Val200-Asn425-Lys432	(1261) (1249)	GIGCALCGS CAGANGS COCHOSTICALS ALG
Vall20-Ile201-Ile424-Ala433	(1243) (1237)	GIGCAGCGCGAGAAGCGCGCCCCCCG
Vall20-Ile2018-Ile424-Ala433	(1237)	GREEN CONTRACTOR CONTRACTOR
Consensus	(1291)	CTCONCOCCONONACCCCCCCTTCACCCTG
Consensus	(1291)	GTGCAGCGCGAGAAGCGCGCCGTGACCCTG 1321 - 1350
Leu122-Ser199 Tryp427-Gly431	(1291)	1321 - 1350 Geografie - 1350
Vall27-Asn195-Arg426-Gly431	(1321)	GGCB CARL TREET GGCTT CTGCC GCC
Vall20-Thr202-Ile424-Ala433	(1267)	GCC TO THE PROPERTY OF THE CONTROL O
Leu122-Ser199-Arg426-Lys432	(1291)	G TO THE CONTROL OF T
Leu122-Ser199-Arg426-Gly431		
	(1291)	GGGGCGAVERNICE (GGGCCCCCCCCCCGGGC
Lys121-Val200-Asn425-Lys432 Val120-Ile201-Ile424-Ala433	(1279)	GGCGCEATCTTECTGGGGTTTCCTTGGCGCC
Vall20-11e201-11e424-Ala433 Vall20-11e201B-11e424-Ala433	(1267)	ECCONTRACTORECTIVO TECECOCO
	(1267)	GGCGCATEPTCCTCGGCTTCCTGGGCCCC
Consensus	(1321)	GGCGCCATGTTCCTGGGCTTCCTGGGCGCC 1351 1380
Leu122-Ser199 Tryp427-Gly431	/12211	
Val127-Asn195-Arg426-Gly431	(1321)	GCGGGAGCASCATEGGCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
Val120-Ash195-Arg426-G1y431 Val120-Thr202-Ile424-Ala433	(1351)	GCCCEPAGCACTATGGCCCTTTTGCAGCTG
	(1297)	GCCNC ASSACRATE GEOGRAPHIC DESCRIP
Leu122-Ser199-Arg426-Lys432	(1321)	GCC SPEAGCACUSE (GGC GGC GGC GGC GGC GGC GGC
Leu122-Ser199-Arg426-Gly431	(1321)	Score a contract of the contra

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Lys121-Val200-Asn425-Lys432	(1309)	GCCGCAGCACCATGGGCGCCCGCAGCCTG	
Val120-Ile201-Ile424-Ala433	(1297)	GCCGCAGCACCATGGGCGCCCGCAGCCTG	
Val120-Ile201B-Ile424-Ala433	(1297)	GCCGCAGCACCATGGGCGCCCGCAGCCTG	
Consensus	(1351)	GCCGCAGCACCATGGGCGCCCGCAGCCTG	
001.501.505	(1331)	1381 1410	
Leu122-Ser199 Tryp427-Gly431	(1351)	ACCCTGACCGTGCAGGCCCGCCAGCTGCTG	
Vall27-Asn195-Arg426-Gly431	(1381)	ACCCTGAÇCGTGCAGGCCGCCAGGTGCTG	
Val120-Thr202-Ile424-Ala433	(1327)	ACCCTGACCGTGCAGGCCCCCCAGGTGCTG	
Leu122-Ser199-Arg426-Lys432		ACCCTGACCGTGCAGGCCCGCCAGCTGCTG	
	(1351)	and the first of the control of the	
Leu122-Ser199-Arg426-Gly431	(1351)	ACCCIGACCGTGCAGGCCCGCCAGCTGCTG	
Lys121-Val200-Asn425-Lys432	(1339)	ACCCTGACCGTGCAGCCGCCAGCTGCTG	
Vall20-Ile201-Ile424-Ala433	(1327)	ACCETGACCETGCAGCCCGCCAGCTGCTG	
Vall20-Ile201B-Ile424-Ala433	(1327)	ACCCTGACCGTGCAGGCCCGCCAGCTGCTG	
Consensus	(1381)	ACCCTGACCGTGCAGGCCCGCCAGCTGCTG	
		1411 1440	
Leul22-Ser199 Tryp427-Gly431	(1381)	AGCGGCATCGTGCAGCAGCAGCAACCTG	
Val127-Asn195-Arg426-Gly431	(1411)	AGCGGCATCGTGCAGCAGCAGCAACCTG	
Val120-Thr202-Ile424-Ala433	(1357)	AGCGGCATCGTGCAGCAGCAGCAACCATG	
Leu122-Ser199-Arg426-Lys432	(1381)	AGCGGCATCGTGCAGCAGCAGCAGCACCTG	
Leu122-Ser199-Arg426-Gly431	(1381)	AGCGGCATCGTGCAGCAGCAGCACCACCTG	
Lys121-Val200-Asn425-Lys432	(1369)	AGCGGCATCGTGCAGCAGCAGCACCTG	
Val120-Ile201-Ile424-Ala433	(1357)	AGCGGGATCGTGCAGCAGCAGCAACCTG	
Val120-Ile201B-Ile424-Ala433	(1357)	AGCGGCATCGTGCAGCAGCAGCAACCAGCTG	
Consensus	(1411)	AGCGGCATCGTGCAGCAGCAGCAACCTG	
		1441 1470	
Leu122-Ser199 Tryp427-Gly431	(1411)	CTGGGGGGATEGAGGCCCAGCAGCACCTG	
Val127-Asn195-Arg426-Gly431	(1441)	CTGGGGGGATGGAGGAGGAGGAGGAGGAGGAGGAGGAGGAG	
Val120-Thr202-Ile424-Ala433	(1387)	CTGEGGGCATEGAGGCCCAGCAGCACCTG	
Leu122-Ser199-Arg426-Lys432	(1411)	CTGCCCGCATTCGAGGCCCAGCAGCACCTG	
Leu122-Ser199-Arg426-G1y431	(1411)	CTGGGGGATEGAGGGGGGAGCAGCAGCTG	
Lys121-Val200-Asn425-Lys432	(1399)	CTGCGGGCATGGAGGCCCAGCAGCAGCTG	
Val120-Ile201-Ile424-Ala433	(1387)	CTGCGCGCATGGAGGCCCCAGCAGCACCTG	
Val120-Ile201B-Ile424-Ala433	(1387)	CTGGGGGCATCGAGGCCCAGCAGCACCTG	
Consensus	(1441)	CTGCGCGCCATCGAGGCCCAGCAGCACCTG	
000	(,	1471 1500	
Leu122-Ser199 Tryp427-Gly431	(1441)	EXECUTE CACCETET GGGGGATCAAGOAG	
Val127-Asn195-Arg426-Gly431	(1471)	entre Acteur entre de la	
Val120-Thr202-Ile424-Ala433	(1417)	CTGCAGCTCACCCTGTGGGGGCAYCAAGGAG	
Leu122-Ser199-Arg426-Lys432	(1441)	ENSEASCHYON SCHGTGGGGCAYCAAGCAG	
Leu122-Ser199-Arg426-Gly431	(1441)	CTGCAGCREECEGTGTGGGGCATCAAGCAG	
Lys121-Val200-Asn425-Lys432	(1429)	CHEGAGERERS GRETGEGGCATGAAGGAG	
Val120-Ile201-Ile424-Ala433	(1423) (1417)	CTGCAGCTGACGTGTGGGGCATCAAGCAG	
Val120-11e201-11e424-Ala433		CTGCAGCTGACCGTGTGGGGCATCAAGCAG	
Consensus	-	CTGCAGCTGACCGTGTGGGGCATCAAGCAG	
Consensus	(14/1)	1501 1530	
Leu122-Ser199 Tryp427-Gly431	(1471)	######################################	
Vall27-Asn195-Arg426-Gly431		CTSCAGG CCGGGTGCAGGC	
Vall20-Thr202-Ile424-Ala433			
		Calca (Cca acac) les reception (caec	
		ਭਾਵਰ ਾ ਦਰਜ਼ਵਾ ਂ ਦਰਜ਼ਵਾਜ਼ ਦਰਜ਼ਵਾਜ਼ ਮੁਹਤਾਜ਼ ਦ	
		ETCOAGGO SEEGRESTEGEGGGGGACGGC	
Lys121-Va1200-Asn425-Lys432		CTGCAGGGGGGGGTGGAGGGC	
		CIGCAGGCCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	
		CTGCAGGCCCGCGTGGTGGAGCGC	
Consensus	(1501)	CTGCAGGCCGCGTGCTGGCCGTGGAGCGC	
		1531 1560	
		TACCTGAAGGACCAGCAGCTGCTGGGCATC	
Val127-Asn195-Arg426-Gly431	(1531)	TACETGAAGGACCAGCAGCTGCTGGGCATC	

Val120-Ile201-Ile424-Ala433 Val120-Ile201B-Ile424-Ala433

Consensus

(1627) Grund Stroke Critical Control of Cont

(1627) GACASCTACACCAACCTGATCTACACCCTG

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. 100 0 · · · 100 m· · · · 407 0 · · 431	(1601)	1711	1740
Leu122-Ser199 Tryp427-Gly431 Val127-Asn195-Arg426-Gly431	(1681) (1711)		gecagaaccagcagcagaa gecagaaccagcaggagaa
Val120-Thr202-Ile424-Ala433	(1657)		GECAGAACCAGCAGGAGAAG
Leu122-Ser199-Arg426-Lys432	(1681)	· · · · · · · · · · · · · · · · · · ·	CCCAGAACCAGCAGAAAG
Leu122-Ser199-Arg426-Gly431	(1681)		GCCAGAACCAGCAGCAGAAG
Lys121-Val200-Asn425-Lys432	(1669)		GCAGAACCAGCAGAGAAG
Val120-Ile201-Ile424-Ala433	(1657)	COLUMN TO SERVICE STATEMENT AND ASSESSED TO SERVICE STATEMENT	GCCAGAACCAGCAGCAGAAG
Val120-Ile201B-Ile424-Ala433	(1657)	· Although and the comments of	GCCAGAACCAGCAGGAGAAG
Consensus	(1711)		GCCAGAACCAGCAGGAGAAG
0000045	(1/11/	1741	1770
Leu122-Ser199 Tryp427-Gly431	(1711)		AGCTGCTGGAGCTGGACAAG
Val127-Asn195-Arg426-Gly431	(1741)		AGCTGCTGGAGCAAG
Val120-Thr202-Ile424-Ala433	(1687)		AGCTGCTGGAGCAAG
Leu122-Ser199-Arg426-Lys432	(1711)		AGCTGCTGGAGCTAG
Leu122-Ser199-Arg426-Gly431	(1711)	AACGAGCAGG	agctgctggagctggacaag
Lys121-Val200-Asn425-Lys432	(1699)		AGCTGCTGGAGCTGGACAAG
Val120-Ile201-Ile424-Ala433	(1687)	AACGAGCAGG	AGCTGCTGGAGCAAG
Val120-Ile201B-Ile424-Ala433	(1687)	AACGAGCAGG	AGCTGCTGGAGCAAG
Consensus	(1741)	AACGAGCAGG	AGCTGCTGGAGCTGGACAAG
		1771	1800
Leu122-Ser199 Tryp427-Gly431	(1741)		TGTGGAACTGGTTCGAGATC
Val127-Asn195-Arg426-Gly431	(1771)		<u>TGTGGAAÇTGGTTCGACA</u> TC
Val120-Thr202-Ile424-Ala433	(1717)	redesel/coc	<u>TGTGGAACTGGTTCGACATC</u>
Leu122-Ser199-Arg426-Lys432	(1741)		TGTGGAACTGGTTEGACATC
Leu122-Ser199-Arg426-Gly431	(1741)		IGTGGAACIGGTT <u>CGACAT</u> C
Lys121-Val200-Asn425-Lys432	(1729)		TGTGGAACTGGTTCGALATC
Val120-Ile201-Ile424-Ala433	(1717)	A THE A P. LEWIS CO., LANSING MICHIGAN AND PROPERTY AND P	TGTGGAACTGGTTGGACATC
Val120-Ile201B-Ile424-Ala433	(1717)	And with the course and an extension of the course	TGTGGAACTGGTTCGACATC
Consensus	(1771)		TGTGGAACTGGTTCGACATC
I 0.122 Co.=100 Trum427 Clu421	(1771)	1801	1830 TGTGGTACATÇAAGATCITC
Leu122-Ser199 Tryp427-Gly431 Val127-Asn195-Arg426-Gly431	(1771) (1801)		TGTGGTACATCAAGATCZTC
Val120-Thr202-Ile424-Ala433	(1747)		COLUMN TO A CANCER C
Leu122-Ser199-Arg426-Lys432	(1771)		GEGGTACATCAACATCETC
Leu122-Ser199-Arg426-Gly431	(1771)		RETGETACATOA CANCETO
Lys121-Val200-Asn425-Lys432	(1759)		POPECTA AND VOLVE AND THE
Vall20-Ile201-Ile424-Ala433	(1747)	Company of the Party of the Par	EGEGGTACATCAAGATEUEC
Val120-Ile201B-Ile424-Ala433	(1747)		TGTGGTACATCAAGATCATC
Consensus	(1801)		TGTGGTACATCAAGATCTTC
	, ,	1831	1860
Leu122-Ser199 Tryp427-Gly431	(1801)	HAMITE CONTOC	REGEGGGERIGETTE GEGERATE
Val127-Asn195-Arg426-Gly431	(1831)	AND STATE OF THE C	regeeggeetesteseelig
Val120-Thr202-Ile424-Ala433	(1777)		୲ଽ୶ ମ୍ବର୍ମ୍ବର ଓ ଟ୍ଟୋଟ୍ଟ୍ର
Leu122-Ser199-Arg426-Lys432	(1801)		हिल्लाहरू <mark>त्वलक्षात्वस्</mark> र हेन्द्र स्टब्स्
Leu122-Ser199-Arg426-Gly431	(1801)		ମ୍ୟର୍ଗ୍ୟ କ୍ରେମ୍ବର ଜଣ୍ଡ ହେ ଏହି
Lys121-Va1200-Asn425-Lys432	(1789)		redicecencenses cue
Val120-Ile201-Ile424-Ala433	(1777)		TGGGCGCCTGGTGGGCCTG
Vall20-Ile201B-Ile424-Ala433	(1777)	The second secon	HGEGGGGGLGGLGGGG SAIC
Consensus	(1831)		TGGGCGGCCTGGTGGGCCTG
	(1000)	1861	1890
Leu122-Ser199 Tryp427-Gly431	(1831)		TCACCGTGCTGAGCATCGTG
Val127-Asn195-Arg426-Gly431	(1861)		TCACCGTGCTGAGCATCGTG
Val120-Thr202-Ile424-Ala433	(1807)		TCACCGTGCTGAGCATCGTG
Leu122-Ser199-Arg426-Lys432	(1831)		TCACCGTGCTGAGCATCGTG
Leu122-Ser199-Arg426-Gly431	(1831)		TCACCGTGCTGAGCATCGTG
Lys121-Va1200-Asn425-Lys432	(1819)	CGCATCGTGT	TCACCGTGCTGAGCATCGTG

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Val120-Ile201-Ile424-Ala433
                                      (1807) CGCATCGTGTTCACCGTGCTGAGCATCGTG
  Val120-Ile201B-Ile424-Ala433
                                      (1807) CGCATCGTGTTCACCGTGCTGAGCATECTG
                        Consensus
                                      (1861) CGCATCGTGTTCACCGTGCTGAGCATCGTG
 Leu122-Ser199 Tryp427-Gly431
                                      (1861) AACCGCGTGCGCCAGGGCTACAGCCCCCTG
   Val127-Asn195-Arg426-Gly431
                                     (1891) AACCGCGTGCGCCAGGGCTACAGCCCCCTG
                                     (1837) AACCGCGTGCGCCAGGGCTACAGECCCCTG
  Val120-Thr202-Ile424-Ala433
  Leu122-Ser199-Arg426-Lys432
                                     (1861) AACCGCGTGCGCCAGGGCTACAGCCCCCTG
(1861) AACGGCGTGCGCCAGGGCTACAGCCCCGTG
  Leu122-Ser199-Arg426-Gly431
  Lys121-Val200-Asn425-Lys432
                                     (1849) AACEGCGTECGCCAGGGCTACAGCCCCCCCG
  Val120-Ile201-Ile424-Ala433
                                     (1837) BACCGCGIGGGCCAGGGCTACAGCCCCCTG
 Val120-Ile201B-Ile424-Ala433
                                     (1837) AACCGCGTGCCCAGGGCTACAGCCCCCTG
                       Consensus
                                     (1891) AACCGCGTGCGCCAGGGCTACAGCCCCCTG
 Leu122-Ser199 Tryp427-Gly431
                                     (1891) AGCTTCCAGACCCGCTTCCCCGCCCCCGGC
  Val127-Asn195-Arg426-Gly431
                                     (1921) AGCTTCCAGACCCGGTTCCCCGCCCCCCC
                                     (1867) AGETTCCAGACCCGCTTCCCCGGCCCCCCC
  Val120-Thr202-Ile424-Ala433
  Leu122-Ser199-Arg426-Lys432
                                     (1891) AGCTICCAGAGEGGCTTCCCGGCCGGGGC
  Leu122-Ser199-Arg426-Gly431
                                     (1891) AGCTTCCAGACGCGCTTCCCCGCGCCCCCCC
  Lys121-Val200-Asn425-Lys432
                                     (1879) AGCTTCCAGACCCGCTTCCCCGCCCCCCC
                                     (1867) AGCTICCAGACCCGCTTCCGCGCCCCCGCGC
  Val120-Ile201-Ile424-Ala433
 Val120-Ile201B-Ile424-Ala433
                                     (1867) AGGTTECAGAGGGGGTTTECGGGGGGGGGGG
                                     (1921) AGCTTCCAGACCCGCTTCCCGGCCCCCGC
                       Consensus
 Leu122-Ser199 Tryp427-Gly431
                                     (1921) GGCCCCGACCGCCCGAGGGCATCGAGGAG
                                     (1951) GGCCCGACGGCCCGAGGGC)TICGAGGAG
  Val127-Asn195-Arg426-Gly431
  Val120-Thr202-Ile424-Ala433
                                     (1897) GGCCCCGASCCSGCGAGGCAVCGAGGAG
  Leu122-Ser199-Arg426-Lys432
                                            GGCCCCGACCGCCCGAGGGCATCCAGGGG
                                     (1921)
 Leu122-Ser199-Arg426-Gly431
                                            GCର କ୍ଷେତ୍ର ଜଣ ବ୍ୟର୍ଥରେ ମଧ୍ୟର କମ୍ମାନ୍ତ ନ୍ୟାନ୍ତ
                                     (1921)
 Lys121-Val200-Asn425-Lys432
                                             त्त्रं वस्त्रं ता हिंदि स्वर्थक स्वरं स्वरं क्षेत्रं विकास स्वरं स्वरं स्वरं स्वरं स्वरं स्वरं स्वरं स्वरं स्व
                                     (1909)
 Val120-Ile201-Ile424-Ala433
                                    (1897)
                                             विवर्गक्षकार्ष्ट्रस्त १००० विश्वतिकार्यस्त सम्भागन्ति ।
Val120-Ile201B-Ile424-Ala433
                                    (1897)
                                            त्तर्वक्षकाम् (क्षान्त्रभवकृत्यः शत्स्वमा भावसः (स्
                       Consensus
                                    (1951)
                                            GGCCCCGACCCCCGAGGGCATCGAGGAG
Leu122-Ser199 Tryp427-Gly431
                                    (1951)
                                            त्रात्रध्ये<mark>वेत्</mark>त्रवार्थ्यम् । स्वत्र
 Val127-Asn195-Arg426-Gly431
                                    (1981)
                                            GAGGCCGCCACCCACCCACCCACCCACCC
 Val120-Thr202-Ile424-Ala433
                                    (1927)
                                            त् १९८५५५५५५ । १९८५ । १९८५ । १९८५ । १९<mark>७</mark>
 Leu122-Ser199-Arg426-Lys432
                                    (1951)
                                            द्रभावनात्रभावस्थान्। अवद्रश्चनात्रभावस्थान्। अवद्रश्चनाः अव
 Leu122-Ser199-Arg426-Gly431
                                            चित्रवत्त्रवस्त्रवस्त्रवस्त्रवस्त्रवस्त्रस्य स्टब्स्स्स्य स्टब्स्स्स्य स्टब्स्स्स्य स्टब्स्स्य स्टब्स्स्य स्टब्स्स्य
                                    (1951)
 Lys121-Val200-Asn425-Lys432
                                            त्रम् तत्त्वात्रवाद्यवाद्यम् अवस्य स्थात्त्रवाद्यम् अत्
                                    (1939)
 Val120-Ile201-Ile424-Ala433
                                    (1927)
                                            क्तः स्टार्चस्य स्थाने विश्वस्थाने स्थाने स्थान
Val120-Ile201B-Ile424-Ala433
                                    (1927)
                                            तः।तरहन्तित्वस्याधिति।तः।व्यानिकः।व्यानिकः।
                                    (1981) GAGGGCGGCGACCGCACCGCAGC
                      Consensus
Leu122-Ser199 Tryp427-Gly431
                                            ः(यं अंशव अभेशक्षेत्र स्थानः । अंदर्शक्षेत्र स्थाप्त स्थाप्त स्थाप्त स्थापित स्थाप्त स्थापित स्थापित स्थापित स
                                    (1981)
 Val127-Asn195-Arg426-Gly431
                                    (2011) PERMETORICALES PERMETENCE CONTRACTOR
 Val120-Thr202-Ile424-Ala433
                                            <u>Vegene Greek en foltgeskielen ertogs</u>e
                                    (1957)
 Leu122-Ser199-Arg426-Lys432
                                    (1981) AGEGGCCTGGTGGACGGCCTGGTGGGGGGGGG
 Leu122-Ser199-Arg426-Gly431
                                    (1981) AGECECCTIEFTE AGEC TREGTERE
 Lys121-Val200-Asn425-Lys432
                                    (1969) AGGING प्रमाद कार्य कार्य द्वार कार्य कार्य कार्य करता है
 Val120-Ile201-Ile424-Ala433
                                    (1957) AGECCCTEG/GCACGGCGTGCTGCCCTG
Val120-Ile201B-Ile424-Ala433
                                    (1957) AGCCCCCTGCTGCACGGGCCGGTGGCCGTG
                      Consensus
                                    (2011) AGCCCCTGGTGCACGGCCTGCTGGCCCTG
                                            2041
Leul22-Ser199 Tryp427-Gly431
                                    (2011) Andred averaged averaged
 Val127-Asn195-Arg426-Gly431
                                   (2041) अर्भाद्यवस्थान्त्राह्यस्थान्त्राहरूत्वाहरू
 Val120-Thr202-Ile424-Ala433
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Leu122-Ser199-Arg426-Lys432	(2011)	ATCTGGGACG	ACCTGCGCAGCCTGTGGCTG
Leu122-Ser199-Arg426-G1y431	(2011)	ATCTGGGACC	ACCTGCGCAGCCTGTGCCTG
Lys121-Val200-Asn425-Lys432	(1999)	The second secon	ACCTGCGCAGCCTGTGCGTG
Val120-Ile201-Ile424-Ala433	(1987)	A STATE OF THE PERSON AS A PER	ACCTGCGCAGCCTGTGCCTG
Val120-Ile201B-Ile424-Ala433	(1987)		ACCTGCGCAGCCTGTGCCTG
Consensus	(2041)		ACCTGCGCAGCCTGTGCCTG
	(2011)	2071	2100
Leu122-Ser199 Tryp427-Gly431	(2041)		ACCECCTECECGACCTGATC
Val127-Asn195-Arg426-Gly431	(2071)		CCGCCTGCGCGACCTGATC
Val120-Thr202-Ile424-Ala433	(2017)		CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC
Leu122-Ser199-Arg426-Lys432	(2041)		CEGCETECECGACCTGATC
Leu122-Ser199-Arg426-Gly431	(2041)		TOGGOTGUEGACUTGATO
Lys121-Val200-Asn425-Lys432	(2029)		COGCON COCCACCA CON CO
Val120-Ile201-Ile424-Ala433	(2017)		WEST CONFIDENCE OF THE PROPERTY OF THE PROPERT
Vall20-Ile201B-Ile424-Ala433	(2017)		VECGCETGEGEGACETGATC
Consensus	(2017)		ACCGCCTGCGCGACCTGATC
Consensus	(20/1)	2101	
Leu122-Ser199 Tryp427-Gly431	(2071)		2130
Val127-Asn195-Arg426-Gly431		CIGALEGUEGE	CCCCATEGIGGAGCIGCTG
Val120-Thr202-Ile424-Ala433	(2101)	CIGATOGCCGC	eccatesteracterie
Leu122-Ser199-Arg426-Lys432	(2047)		<u>Eccentretegacticate</u>
Leu122-Ser199-Arg426-Eys432	(2071)		<u>्रवटान्त्रीतः इत्यरदास् (द्वारास्त्रास्</u> ट
Lys121-Val200-Asn425-Lys432	(2071)		eccatestissauchisms
Val120-Ile201-Ile424-Ala433	(2059)		ecconicci <u>ccaccicci</u> c
Val120-11e201-11e424-Ala433 Val120-11e201B-11e424-Ala433	(2047)		<u>ecgcategregaecter</u> e
	(2047)		GGGCAT & STIGGAGGTTGGTG
Consensus	(2101)		CCGCATCGTGGAGCTGCTG
Tou122-Sow100 March 427 G1 421		2131	2160
Leu122-Ser199 Tryp427-Gly431	(2101)	GGCCGCCGCGG	CTGGGACGCCCTGAAGTAC
Val127-Asn195-Arg426-Gly431	(2131)	GGCCGCCGCG	CTGGGAGGGCCTGAAGTAC
Val120-Thr202-Ile424-Ala433	(2077)	CCCCCCCCCCCC	Ltggg NggcC CIGAAGTAC
Leu122-Ser199-Arg426-Lys432	(2101)	CCCCCCCCCCC	Crecerced Cucha Carac
Leu122-Ser199-Arg426-Gly431	(2101)	cic of sich sich sich	GREGER GEOGRAPH GRAC
Lys121-Val200-Asn425-Lys432	(2089)	Redect to Collec	STREETHERSON CHATCHE
Val120-Ile201-Ile424-Ala433	(2077)		enderace envious
Vall20-Ile201B-Ile424-Ala433	(2077)		eneggy elegent (Amena e
Consensus	(2131)		CTGGGAGGCCCTGAAGTAC
. 100 - 100 - 100		2161	2190
Leu122-Ser199 Tryp427-Gly431	(2131)		Concestors) or accessors
Val127-Asn195-Arg426-Gly431	(2161)		GENERACH MENGEN CONTRACTOR
Val120-Thr202-Ile424-Ala433	(2107)		Contide to the contract the second
Leu122-Ser199-Arg426-Lys432	(2131)	Redeless Avecas	clented version relevants or it
Leu122-Ser199-Arg426-Gly431	(2131)		नुष्टात्तः (६००) का स्तत् गास्त्रका (६
Lys121-Val200-Asn425-Lys432	(2119)		elegicology and actual contractions
Val120-Ile201-Ile424-Ala433	(2107)		cleric arteration (clericia) c
Val120-Ile201B-Ile424-Ala433	(2107)		Cettgo ago a conserve ag
Consensus	(2161)		GCTGCAGTACTGGATCCAG
	•	2191	2220
Leu122-Ser199 Tryp427-Gly431			SACCCOCCITCACCCARCATIC
Val127-Asn195-Arg426-Gly431	(2191)		MAGGGGGGTGAGGGTGTVEC
Val120-Thr202-Ile424-Ala433	(2137)	GAGC TGAAGAA	AGCGCCGTGAGGCAGGTAC
Leul22-Ser199-Arg426-Lys432	(2161)		AGEGECETGAGECTIGTEC
Leu122-Ser199-Arg426-Gly431			AGCGCCTGAGCCTGTTC
Lys121-Val200-Asn425-Lys432	(2149)	GAGCTGAAGAA	ACCCCCTGAGCCTGTTC
Val120-Ile201-Ile424-Ala433	(2137)	GAGCTGAAGAA	AGCGCCGTGAGCCTGTTC
Vall20-Ile201B-Ile424-Ala433	(2137)	GAGCTGAAGAA	AGCGCCTGAGCCTGTTC
Consensus			AGCGCCGTGAGCCTGTTC
		2221	2250

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Leu122-Ser199 Tryp427-Gly431	(2191)	Grees Historia Control of the Contro
Val127-Asn195-Arg426-Gly431	(2221)	GACGCCT RECEASEGE GTGGCCGAGGCC
Val120-Thr202-Ile424-Ala433	(2167)	CACCCC TRACCCALCCCCTTCCCCAACCCC
Leu122-Ser199-Arg426-Lys432	(2191)	CYOCA OFFICE AND COOR ACCOUNTING
Leu122-Ser199-Arg426-Gly431	(2191)	CYOCK MINTERSTATED COCCINCLOS CASCOC
Lys121-Val200-Asn425-Lys432	(2179)	GAGGC WANGE COANGE COEFF GEOCGAGE CC
Val120-Ile201-Ile424-Ala433	(2167)	
Val120-Ile201B-Ile424-Ala433	(2167)	
Consensus	(2221)	
	, ,	2251 2280
Leu122-Ser199 Tryp427-Gly431	(2221)	
Val127-Asn195-Arg426-Gly431	(2251)	
Val120-Thr202-Ile424-Ala433	(2197)	
Leu122-Ser199-Arg426-Lys432	(2221)	
Leu122-Ser199-Arg426-Gly431	(2221)	
Lys121-Val200-Asn425-Lys432	(2209)	
Val120-Ile201-Ile424-Ala433	(2197)	
Val120-Ile201B-Ile424-Ala433	(2197)	
Consensus	(2251)	
		2281 2310
Leu122-Ser199 Tryp427-Gly431	(2251)	AVOGGEOGEGETTECTGCACATECCCEGC
Val127-Asn195-Arg426-Gly431	(2281)	ATGREE GEGEOTTECT GCACATECCCCGC
Val120-Thr202-Ile424-Ala433	(2227)	ALCOUR GREET CATEGORICA CATEGORIC
Leu122-Ser199-Arg426-Lys432	(2251)	ATCECOSCECCTROCTGCACATCCCCCGC
Leu122-Ser199-Arg426-Gly431	(2251)	AT GGGGGGGGTT COTGCAGANGCCCCCGC
Lys121-Val200-Asn425-Lys432 Val120-Ile201-Ile424-Ala433	(2239)	Vreceegesemmenter/ovinedence
Val120-11e2019-11e424-Ala433	(2227)	ATCGGECGGGCTTCCTGCACATOCCOCGC
Consensus	(2227) (2281)	ATEGGCEGCECTTCCTGCACATECCCEGC
Consensus	(2201)	ATCGGCCGCGCCTTCCTGCACATCCCCCGC 2311 2340
Leu122-Ser199 Tryp427-Gly431	(2281)	2311 2340
Val127-Asn195-Arg426-Gly431	(2311)	COMMISSION AGGINT CONTROL CONT
Val120-Thr202-Ile424-Ala433	(2257)	୭୯୭ : (୭୯୯ : (୬) (୮/୯୯୭) : GA/୯୮୭ ପ୍ରତ୍ୟର : ୧୯୮୭
Leu122-Ser199-Arg426-Lys432	(2281)	ब्रुचक ११० अन्यत्व स्ट्रास्ट्रम्स्ट्रियाचे साम्ब्रुच्याच्या । इस्ट्रियम्
Leu122-Ser199-Arg426-Gly431	(2281)	୶ଽଢ଼୕ଽଽଡ଼୰୕୷ଢ଼୕୕ୡ୕ୠୠ୷ୠ୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷୷
Lys121-Val200-Asn425-Lys432	(2269)	e comparison completes and construction of the
Val120-Ile201-Ile424-Ala433		SHOLY CONTROL CONTROL WAS A CONTROL OF STREET
Vall20-Ile201B-Ile424-Ala433		ଜିନ୍ଦ୍ର ମଧ୍ୟ ପ୍ରମିତ୍ୟ (ପ୍ରମୁକ୍ତ ହାଣ୍ଡିକ ପ୍ରମୁକ୍ତ ପ୍ରମୁକ୍ତ ହେ ।
Consensus	(2311)	
	,,	2341 2352
Leu122-Ser199 Tryp427-Gly431	(2311)	294 Cy 2. 4. (Gy 3 Gr C) . (G
Val127-Asn195-Arg426-Gly431	(2341)	<u>ૄૹ૽ૡૡ૾ૹ૽ૹ૾૽ૹૼૡઌ૽ૡૹૻૡ૽૽ૺૺૹ</u>
Val120-Thr202-Ile424-Ala433	(2287)	CHICE SECTION OF TO
Leu122-Ser199-Arg426-Lys432	(2311)	534.64 (\$ 576.84 (# 1.1 1.7 2
Leu122-Ser199-Arg426-Gly431	(2311)	અપુ લ્ લાકુકુ (ત્સુપંદ્રાલ) , ૧૯
Lys121-Va1200-Asn425-Lys432	(2299)	eakerkielekkon). Co
Val120-Ile201-Ile424-Ala433	(2287)	CHARLASTA CONTRACTOR
Val120-Ile201B-Ile424-Ala433	(2287)	CIGTINGICGAC
Consensus	(2341)	CTGTAACTCGAG

SEQ ID NO:3 VAL120-ALA204

GTCTTCGTTTCGCCCAGCGCCGTGGAGAAGCTGTGGGTGACCGTGTACTACGGCGTGCCCGTG TGGAAGGAGGCCACCACCACCTGTTCTGCGCCAGCGACGCCAAGGCCTACGACACCGAGGT GCACAACGTGTGGGCCACCCACGCCTGCGTGCCCACCGACCCCAACCCCCAGGAGATCGTGCT GGAGAACGTGACCGAGAACTTCAACATGTGGAAGAACAACATGGTGGAGCAGATGCACGAG GACATCATCAGCCTGTGGGACCAGAGCCTGAAGCCCTGCGTGGGCGCCGGCGCCTGCCCCAA GGTGAGCTTCGAGCCCATCCCCATCACTACTGCGCCCCGCCGGCTTCGCCATCCTGAAGTG CAACGACAAGAAGTTCAACGGCAGCGGCCCCTGCACCAACGTGAGCACCGTGCAGTGCACCC ACGGCATCCGCCCGTGGTGAGCACCCAGCTGCTGAACGGCAGCCTGGCCGAGGAGGGC GTGGTGATCCGCAGCGAGAACTTCACCGACAACGCCAAGACCATCATCGTGCAGCTGAAGGA GAGCGTGGAGATCAACTGCACCCGCCCAACAACAACACCCGCAAGAGCATCACCATCGGCC CCGGCCGCCTTCTACGCCACCGGCGACATCATCGGCGACATCCGCCAGGCCCACTGCAACA TCAGCGGCGAGAAGTGGAACAACACCCTGAAGCAGATCGTGACCAAGCTGCAGGCCCAGTTC GGCAACAAGACCATCGTGTTCAAGCAGAGCAGCGGCGGCGACCCCGAGATCGTGATGCACAG CTTCAACTGCGGCGGCGAGTTCTTCTACTGCAACAGCACCCAGCTGTTCAACAGCACCTGGAA CAACACCATCGGCCCCAACACACCCAACGGCACCATCACCCTGCCCTGCCGCATCAAGCAGA TCATCAACCGCTGGCAGGAGGTGGGCAAGGCCATGTACGCCCCCCCATCCGCGGCCAGATC CGCTGCAGCAGCAACATCACCGGCCTGCTGCTGACCCGCGACGGCGGCAAGGAGATCAGCAA CACCACCGAGATCTTCCGCCCCGGCGGCGCGACATGCGCGACAACTGGCGCAGCGAGCTGT GTGGTGCAGCGCGAGAAGCGCGCCGTGACCCTGGGCGCCATGTTCCTGGGCTTCCTGGGCGCC GCCGGCAGCACCATGGGCGCCCGCAGCCTGACCCTGACCGTGCAGGCCCGCCAGCTGCTGAG CGGCATCGTGCAGCAGCAGCACACCTGCTGCGCGCCATCGAGGCCCAGCAGCACCTGCTGC AGCTGACCGTGTGGGGCATCAAGCAGCTGCAGGCCCGCGTGCTGGCCGTGGAGCGCTACCTG AAGGACCAGCAGCTGCTGGGCATCTGGGGCTGCAGCGCCAAGCTGATCTGCACCACCGCCGT GCCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGACCAGATCTGGAACAACATGACCTGGA TGGAGTGGGAGCGCGAGATCGACAACTACACCAACCTGATCTACACCCTGATCGAGGAGAGC CAGAACCAGCAGGAGAAGAACGAGCAGGAGCTGCTGGACCAAGTGGGCCAGCCTGT GGAACTGGTTCGACATCAGCAAGTGGCTGTGGTACATCAAGATCTTCATCATGATCGTGGGCG GCCTGGTGGGCCTGCGCATCGTGTTCACCGTGCTGAGCATCGTGAACCGCGTGCGCCAGGGCT ACAGCCCCTGAGCTTCCAGACCCGCTTCCCCGCCCCCGCGGCCCCGACCGCCCCGAGGGCA TCGAGGAGGAGGGCGAGCGCGACCGCACCGCAGCAGCCCCCTGGTGCACGGCCTGCTG GCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCAGCTACCACCGCCTGCGCGACCTG ATCCTGATCGCCGCCCGCATCGTGGAGCTGCTGGGCCCGCGCGGCTGGGAGGCCCTGAAGTAC TGGGGCAACCTGCTGCAGTACTGGATCCAGGAGCTGAAGAACAGCGCCGTGAGCCTGTTCGA CGCCATCGCCATCGCCGTGGCCGAGGGCACCGACCGCATCATCGAGGTGGCCCAGCGCATCG GCCGCGCCTTCCTGCACATCCCCGCCGCATCCGCCAGGGCTTCGAGCGCGCCCTGCTGTAAC **TCGAG**

SEQ ID NO:4 VAL120-ILE201

GTCTTCGTTTCGCCCAGCGCCGTGGAGAAGCTGTGGGTGACCGTGTACTACGGCGTGCCCGTG TGGAAGGAGGCCACCACCACCTGTTCTGCGCCAGCGACGCCAAGGCCTACGACACCGAGGT GCACAACGTGTGGGCCACCCACGCCTGCGTGCCCACCGACCCCCAGGAGATCGTGCT GGAGAACGTGACCGAGAACTTCAACATGTGGAAGAACAACATGGTGGAGCAGATGCACGAG GACATCATCAGCCTGTGGGACCAGAGCCTGAAGCCCTGCGTGGGCGGCATCACCCAGGCCTG CCCCAAGGTGAGCTTCGAGCCCATCCCCATCCACTACTGCGCCCCGCCGGCTTCGCCATCCT GAAGTGCAACGACAAGAAGTTCAACGGCAGCGGCCCCTGCACCAACGTGAGCACCGTGCAGT GCACCCACGCCATCCCCCCGTGGTGAGCACCCAGCTGCTGAACGGCAGCCTGGCCGAG GAGGGCGTGGTGATCCGCAGCGAGAACTTCACCGACAACGCCAAGACCATCATCGTGCAGCT GAAGGAGAGCGTGGAGATCAACTGCACCCGCCCAACAACAACACCCGCAAGAGCATCACCA TCGGCCCGGCCGCCTTCTACGCCACCGGCGACATCATCGGCGACATCCGCCAGGCCCACT GCAACATCAGCGGCGAGAAGTGGAACAACACCCTGAAGCAGATCGTGACCAAGCTGCAGGCC CAGTTCGGCAACAAGACCATCGTGTTCAAGCAGAGCAGCGGCGGCGACCCCGAGATCGTGAT GCACAGCTTCAACTGCGGCGGCGAGTTCTTCTACTGCAACAGCACCCAGCTGTTCAACAGCAC CTGGAACACACCATCGGCCCCAACAACACCCAACGGCACCATCACCCTGCCCTGCCGCATCA CAGATCCGCTGCAGCAGCAACATCACCGGCCTGCTGACCCGCGACGGCGGCAAGGAGAT CAGCAACACCACGAGATCTTCCGCCCGGCGGCGGCGACATGCGCGACAACTGGCGCAGCG AGCTGTACAAGTACAAGGTGGTGAAGATCGAGCCCCTGGGCGTGGCCCCCACCAAGGCCAAG CGCCGCGTGGTGCAGCGCGAGAAGCGCGCCGTGACCCTGGGCGCCATGTTCCTGGGCTTCCTG GGCGCCGCCGCAGCACCATGGGCGCCCGCAGCCTGACCCTGACCGTGCAGGCCCGCCAGCT GCTGAGCGCATCGTGCAGCAGCAGAACAACCTGCTGCGCGCCATCGAGGCCCAGCAGCACC TGCTGCAGCTGACCGTGTGGGGCATCAAGCAGCTGCAGGCCCGCGTGCTGGCCGTGGAGCGC TACCTGAAGGACCAGCAGCTGCTGGGCATCTGGGGCTGCAGCGGCAAGCTGATCTGCACCAC CGCCGTGCCCTGGAACGCCAGCTGGAGCAACAAGAGCCTGGACCAGATCTGGAACAACATGA CCTGGATGGAGTGGGAGCGCGAGATCGACAACTACACCAACCTGATCTACACCCTGATCGAG GAGAGCCAGAACCAGCAGGAGAAGAACGAGCAGGAGCTGGAGCAGGTGGGCCA GCCTGTGGAACTGGTTCGACATCAGCAAGTGGCTGTGGTACATCAAGATCTTCATCATGATCG TGGGCGGCCTGGGGCCTGCGCATCGTGTTCACCGTGCTGAGCATCGTGAACCGCGTGCGCC AGGGCTACAGCCCCTGAGCTTCCAGACCCGCTTCCCCGCCCCCGCGGCCCCGACCGCCCCG CCTGCTGGCCCTGATCTGGGACGACCTGCGCAGCCTGTGCCTGTTCAGCTACCACCGCCTGCG CGACCTGATCCTGATCGCCGCCCGCATCGTGGAGCTGCTGGGCCGCCGCGGCTGGGAGGCCCT GAAGTACTGGGGCAACCTGCTGCAGTACTGGATCCAGGAGCTGAAGAACAGCGCCGTGAGCC TGTTCGACGCCATCGCCATCGCCGTGGCCGAGGCACCGCATCATCGAGGTGGCCCAGC GCATCGGCCGCCCTTCCTGCACATCCCCCGCCGCATCCGCCAGGGCTTCGAGCGCCCCTGC **TGTAACTCGAG**

SEQ ID NO:5 VAL120-ILE201B

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SEQ ID NO:9 TRP427-GLY431

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SEQ ID NO:18: LEU122-SER199; ARG426-GLY431

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SEQ ID NO:19 LEU122-SER199; ARG426-LYS432

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PCT/US99/31272

SEQ ID NO:21 LYS121-VAL200; ASN425-LYS432

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SEQ ID NO:22 VAL120-ILE201; ILE 424-ALA433

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62 / 65

SEQ ID NO:23: VAL120-ILE201B; ILE424-ALA433

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- Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Asn Ser Asn Asn Glu
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- Thr Met Gly Ala Ala Ser Met Thr Leu Thr Val Gln Ala Arg Gln Leu 530 535 540
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- Ala Gln Gln His Leu Leu Gln Leu Thr Val Trp Gly Ile Lys Gln Leu
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- Gln Ala Arg Ile Leu Ala Val Glu Arg Tyr Leu Lys Asp Gln Gln Leu 580 585 590
- Leu Gly Ile Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr Thr Ala Val 595 600 605
- Pro Trp Asn Ala Ser Trp Ser Asn Lys Ser Leu Glu Gln Ile Trp Asn 610 615 620
- His Thr Thr Trp Met Glu Trp Asp Arg Glu Ile Asn Asn Tyr Thr Ser 625 630 635 640
- Leu Ile His Ser Leu Ile Glu Glu Ser Gln Asn Gln Gln Glu Lys Asn 645 650 655
- Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu Trp Asn Trp 660 665 670
- Phe Asn Ile Thr Asn Trp Leu Trp Tyr Ile Lys Leu Phe Ile Met Ile 675 680 685
- Val Gly Gly Leu Val Gly Leu Arg Ile Val Phe Ala Val Leu Ser Ile 690 695 700
- Val Asn Arg Val Arg Gln Gly Tyr Ser Pro Leu Ser Phe Gln Thr His 705 710 715 720
- Leu Pro Thr Pro Arg Gly Pro Asp Arg Pro Glu Gly Ile Glu Glu 725 730 735
- Gly Gly Glu Arg Asp Arg Asp Arg Ser Ile Arg Leu Val Asn Gly Ser
- Leu Ala Leu Ile Trp Asp Asp Leu Arg Ser Leu Cys Leu Phe Ser Tyr 755 760 765
- His Arg Leu Arg Asp Leu Leu Leu Ile Val Thr Arg Ile Val Glu Leu
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- Leu Gly Arg Arg Gly Trp Glu Ala Leu Lys Tyr Trp Trp Asn Leu Leu 785 790 795 800
- Gln Tyr Trp Ser Gln Glu Leu Lys Asn Ser Ala Val Ser Leu Leu Asn 805 810 815
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Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val 50 55 60

His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro 65 70 75 80

Gln Glu Ile Val Leu Glu Asn Val Thr Glu Asn Phe Asn Met Trp Lys 85 90 95

Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp 100 105 110

Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu 115 120 125

His Cys Thr Asn Leu Lys Asn Ala Thr Asn Thr Lys Ser Ser Asn Trp

Lys Glu Met Asp Arg Gly Glu Ile Lys Asn Cys Ser Phe Lys Val Thr

Thr Ser Ile Arg Asn Lys Met Gln Lys Glu Tyr Ala Leu Phe Tyr Lys 165 170 175

Leu Asp Val Val Pro Ile Asp Asn Asp Asn Thr Ser Tyr Lys Leu Ile 180 185 190

Asn Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro Lys Val Ser Phe 195 200 205

Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe Ala Ile Leu 210 215 220

Lys Cys Asn Asp Lys Lys Phe Asn Gly Ser Gly Pro Cys Thr Asn Val 225 230 235 240

Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val Ser Thr Gln 250 Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Gly Val Val Ile Arg Ser Glu Asn Phe Thr Asp Asn Ala Lys Thr Ile Ile Val Gln Leu Lys Glu Ser Val Glu Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr Arg Lys Ser Ile Thr Ile Gly Pro Gly Arg Ala Phe Tyr Ala Thr Gly Asp Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Ile Ser Gly Glu Lys Trp Asn 330 Asn Thr Leu Lys Gln Ile Val Thr Lys Leu Gln Ala Gln Phe Gly Asn 345 Lys Thr Ile Val Phe Lys Gln Ser Ser Gly Gly Asp Pro Glu Ile Val 360 Met His Ser Phe Asn Cys Gly Glu Phe Phe Tyr Cys Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Asn Thr Ile Gly Pro Asn Asn Thr 395 Asn Gly Thr Ile Thr Leu Pro Cys Arg Ile Lys Gln Ile Ile Asn Arg Trp Gln Glu Val Gly Lys Ala Met Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Lys Glu Ile Ser Asn Thr Thr Glu Ile Phe Arg Pro Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val 470 Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Val Thr Leu Gly Ala Met Phe Leu Gly 505 Phe Leu Gly Ala Ala Gly Ser Thr Met Gly Ala Arg Ser Leu Thr Leu 520 Thr Val Gln Ala Arg Gln Leu Leu Ser Gly Ile Val Gln Gln Gln Asn 535 Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu Leu Gln Leu Thr 555

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- Leu Ile Cys Thr Thr Ala Val Pro Trp Asn Ala Ser Trp Ser Asn Lys 595 600 605
- Ser Leu Asp Gln Ile Trp Asn Asn Met Thr Trp Met Glu Trp Glu Arg 610 615 620
- Glu Ile Asp Asn Tyr Thr Asn Leu Ile Tyr Thr Leu Ile Glu Glu Ser 625 630 635 640
- Gln Asn Gln Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys 645 650 655
- Trp Ala Ser Leu Trp Asn Trp Phe Asp Ile Ser Lys Trp Leu Trp Tyr 660 665 670
- Ile Lys Ile Phe Ile Met Ile Val Gly Gly Leu Val Gly Leu Arg Ile 675 680 685
- Val Phe Thr Val Leu Ser Ile Val Asn Arg Val Arg Gln Gly Tyr Ser 690 695 700
- Pro Leu Ser Phe Gln Thr Arg Phe Pro Ala Pro Arg Gly Pro Asp Arg 705 710 715 720
- Pro Glu Gly Ile Glu Glu Glu Gly Gly Glu Arg Asp Arg Asp Arg Ser 725 730 735
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- Ser Leu Cys Leu Phe Ser Tyr His Arg Leu Arg Asp Leu Ile Leu Ile 755 760 765
- Ala Ala Arg Ile Val Glu Leu Leu Gly Arg Arg Gly Trp Glu Ala Leu 770 775 780
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- Ser Ala Val Ser Leu Phe Asp Ala Ile Ala Ile Ala Val Ala Glu Gly 805 810 815
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PCT/US99/31272 WO 00/39303

<223> Description of Artificial Sequence: Trp427-Gly431

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cagatgcacg aggacatcat cagcctgtgg gaccagagcc tgaagccctg cgtgaagctg 360
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agcaactgga aggagatgga ccgcggcgag atcaagaact gcagcttcaa ggtgaccacc 480
agcateegea acaagatgea gaaggagtae geeetgttet acaagetgga egtggtgeee 540
ategacaacg acaacaccag ctacaagetg ateaactgca acaccagegt gateacccag 600
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gccatcctga agtgcaacga caagaagttc aacggcagcg gcccctgcac caacgtgagc 720
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<223> Description of Artificial Sequence: Arg426-Gly431
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accgaggtgc acaacgtgtg ggccacccac gcctgcgtgc ccaccgaccc caacccccag 240

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gccatcctga agtgcaacga caagaagttc aacggcagcg gcccctgcac caacgtgagc 720
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<211> 2541
<212> DNA
<213> Artificial Sequence
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<223> Description of Artificial Sequence: Arg426-Gly431B
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cccgtgtgga aggaggccac caccacctg ttctgcgcca gcgacgccaa ggcctacgac 180
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accccctgt gcgtgaccct gcactgcacc aacctgaaga acgccaccaa caccaagagc 420
agcaactgga aggagatgga ccgcggcgag atcaagaact gcagcttcaa ggtgaccacc 480
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agcatccgca acaagatgca gaaggagtac gccctgttct acaagctgga cgtggtgccc 540

ategacaacg acaacaccag ctacaagctg atcaactgca acaccagcgt gateacccag 600

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<211> 2541
<212> DNA
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Arg426-Lys432
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cccgtgtgga aggaggccac caccaccctg ttctgcgcca gcgacgccaa ggcctacgac 180
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<211> 2535
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<220>
<223> Description of Artificial Sequence: Asn425-Lys432
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cccgtgtgga aggaggccac caccacctg ttctgcgcca gcgacgccaa ggcctacgac 180
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<223> Description of Artificial Sequence: Ile424-Ala433
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<211> 2517
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<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Gln422-Tyr435
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         Arg426-Lys432
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cccgtgtgga aggaggccac caccacctg ttctgcgcca gcgacgccaa ggcctacgac 180
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PCT/US99/31272 WO 00/39303

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<223> Description of Artificial Sequence:
 Val120-Ile201B; Ile424-Ala433

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